ROLE OF FIBREOPTIC BRONCHOSCOPY IN SMEAR NEGATIVE RE-TREATMENT PULMONARY TUBERCULOSIS

Dissertation submitted In Partial Fulfillment of the Requirements for the Degree of

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DEPARTMENT OF PULMONARY MEDICINE

Government Stanley Medical College & Hospital

Chennai-600 001

THE TAMILNADU DR.M.G.R.MEDICAL UNIVERSITY

CHENNAI-600 032

APRIL 2015

CERTIFICATE

This is to certify that the dissertation on **"ROLE OF FIBRE OPTIC BRONCHOSCOPY IN SMEAR NEGATIVE RETREATMENT PULMONARY TUBERCULOSIS"** is a record of research work done by **DR.S.NAVANEETHA KRISHNAN** in partial fulfilment for M.D. (PULMONARY MEDICINE) Examination of the Tamilnadu, Dr.M.G.R.Medical University to be held in April 2015. The period of study is from December 2013 to July 2014.

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CERTIFICATE BY GUIDE

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DECLARATION

I hereby declare that the dissertation entitled **"ROLE OF FIBRE OPTIC BRONCHOSCOPY IN SMEAR NEGATIVE RETREATMENT PULMONARY TUBERCULOSIS"** submitted for the Degree of Doctor of Medicine in M.D., Degree Examination, Branch XVII, PULMONARY MEDICINE is my original work and the dissertation has not formed the basis for the award of any degree, diploma, associate ship, fellowship or similar other titles. It had not been submitted to any other university or Institution for the award of any degree or diploma.

Place: Chennai Signature of the Scholar

Date: **(DR.S.NAVANEETHA KRISHNAN)**

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Language with all elaborations seems to be having limitation especially when it comes to expression of feelings. It is incapable of conveying in words all the emotions and feelings one wants to say.

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CONTENTS

ROLE OF FIBREOPTIC BRONCHOSCOPY IN SMEAR NEGATIVE RE-TREATMENT PULMONARY TUBERCULOSIS

NAVANEETHA KRISHNAN, G. ALLWYN VIJAY, S.P. VENGADA KRISHNARAJ, R.SRIDHAR,

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BACK GROUND:

Diagnosis of sputum smear –negative retreatment pulmonary tuberculosis patients can be challenging and many patients being put on anti-tubercular treatment empirically, leading many time to avoidable risk of drug toxicity, particularly retreatment cases. Fibreoptic bronchoscopy may provide a confirmative and early diagnosis in such patients.

AIMS:

To assess the role of fibreoptic bronchoscopy in the sputum smear –negative Retreatment pulmonary tuberculosis and compare the pre FOB sputum for LPA with FOB wash AFB culture by LJ medium.

MATIERIALS AND METHODS:

This is prospective study. It was conducted on 52, clinically and radio logically suspected sputum smear –negative Retreatment Pulmonary Tuberculosis patients attending Government Hospital of Thoracic Medicine, Tambaram Sanatorium. Fibreoptic bronchoscopy was performed. Bronchial wash and brush sent for AFB smear and malignant cytology. Bronchial wash for AFB culture by LJ medium, post FOB sputum for AFB smear. All patients in this study given pre bronchoscopy sputum for LPA.

RESULTS:

Final diagnosis of sputum smear –negative Retreatment Pulmonary Tuberculosis was made by bronchial wash AFB smear positive – 14/52 (26.92%), bronchial wash AFB Culture by LJ medium – 23/52 (44.23%), bronchial brush for AFB smear positive– 12/52 (23.07%), post FOB Sputum for AFB smear positive – 6/52 (11.53%), FOB brush for malignant cytology - 2/52 (3.85%). Pre bronchoscopy sputum for LPA deduct mycobacterium in 15 patients

15/52(28.84 %),(in which 5 patients LPA positive ,10 patients LPA negative, culture positive). All these patients within the margin of FOB wash AFB culture positive cases. Except one patients whose pre bronchoscopy sputum LPA positive p value <0.001). Bronchial wash Bacterial c/s shows pyogenic infection in 12/52 (23%).

CONCLUSION:

Our study suggests that fibreoptic bronchoscopy can provide useful tool for diagnosis of sputum smear –negative Retreatment Pulmonary Tuberculosis. It may decide the CAT II ATT in these patients. It also diagnosis non tuberculous pathology like malignancy.

KEY WORDS: Bronchial wash and brush, pulmonary tuberculosis, sputum smear negative, fibreoptic bronchoscopy, retreatment cases.

INTRODUCTION

Tuberculosis

Tuberculosis (TB) is a highly infectious bacterial disease caused by Mycobacterium tuberculosis. Any part of the body affected by tuberculosis. Pulmonary Tuberculosis is the commonest form of TB.

Usually TB bacillus spreads through air. When a pulmonary tuberculosis patient sneezes or coughs, tiny droplets containing TB bacilli are spreads in the air. Healthy person who got infection with tuberculosis when she/he inhaled these droplets. The life time risk of developing tuberculosis in these infected people will have a 10%.[1]

10-15 healthy persons infected by a smear positive pulmonary tuberculosis patient in the general people in a year and if these smear positive patients left untreated, they remain infectious for 2 to 3 years.[1]

Tuberculosis burden in global

TB incidence[2]

In 2012, globally estimated TB incident cases about 8.6 million, it was equivalent to 122 cases per lakhs population. The absolute number of incident cases is falling slowly. In 2012 most of the estimated number of cases occurred in African Region (27%) and the Asia (58%);

2 smaller proportions of cases occurred in the European Region (4%), the Eastern Mediterranean Region (8%) and the Region of the Americas (3%). The 22 high burden countries that have been given high incidence cases. In 2012 the largest number of incident cases occurred five countries include China (0.9 million–1.1 million), India (2.0 million–2.4 million), Pakistan (0.3 million–0.5 million), South Africa (0.4 million–0.6 million) and Indonesia (0.4 million–0.5 million).

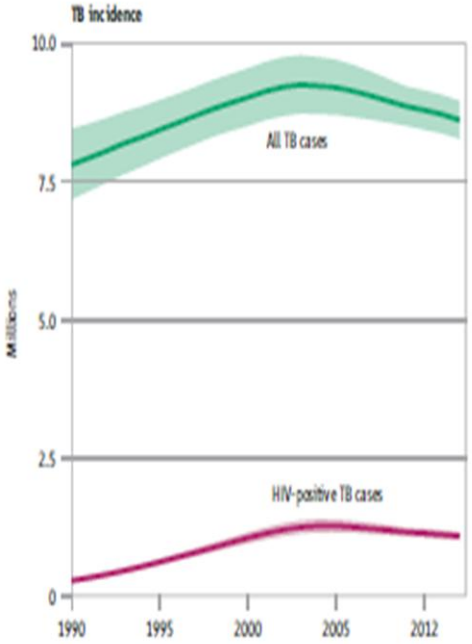
In the 8.6 million incident TB cases in 2012, people living with HIV estimate around 1.0 million–1.2 million (12–14%). About MDR-TB, new cases estimate approximately 450 000 (range, 300 000 to 600 000) in the worldwide by end of 2012. This total includes acquired and primary MDR-TB cases.[2]

Coverage of country consultations on estimates of TB disease burden, 2008–2013

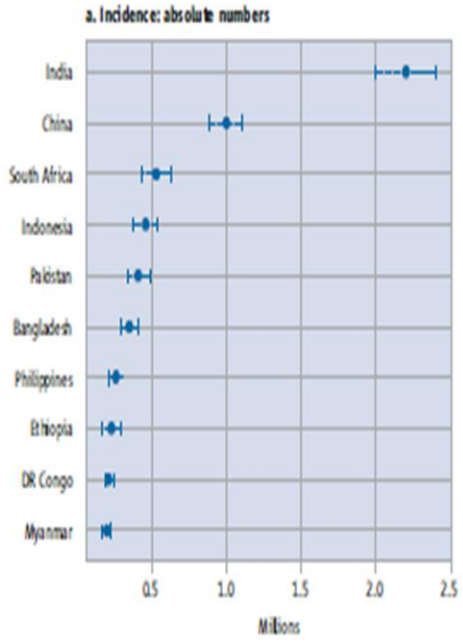
[1] An inventory study can be used to measure the number of cases that are diagnosed but not reported, but using results to estimate the total number of incident cases using capture–recapture methods requires that certain conditions are met. These are explained in a guide on inventory studies recently published by WHO, which is available at: www.who.int/tb/publications/inventory_studies/en/index.html

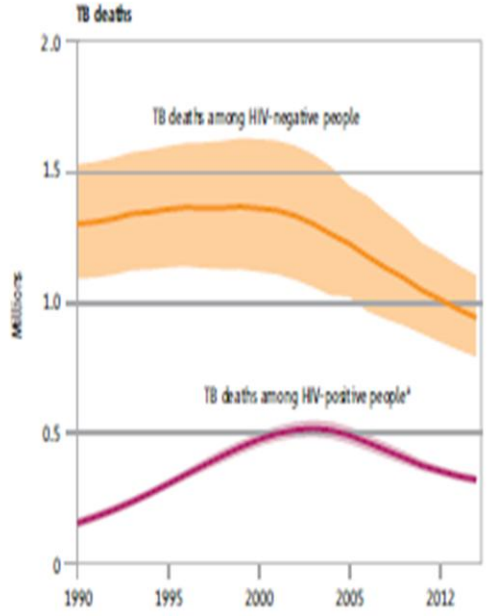
[2] Asia refers to the WHO Regions of South-East Asia and the Western Pacific.

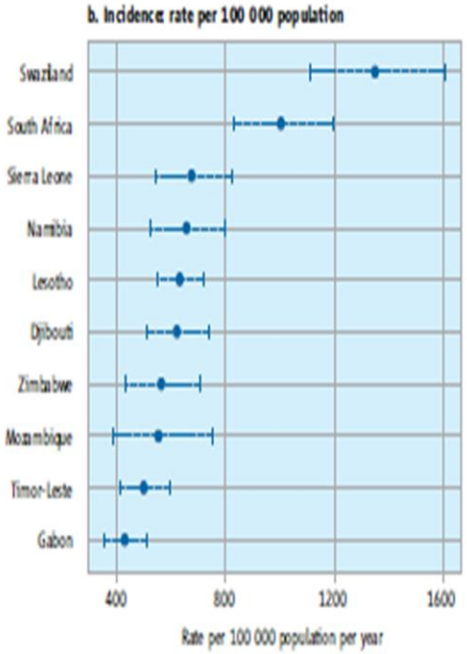
Estimated absolute numbers of TB cases and deaths (in millions), 1990–2012



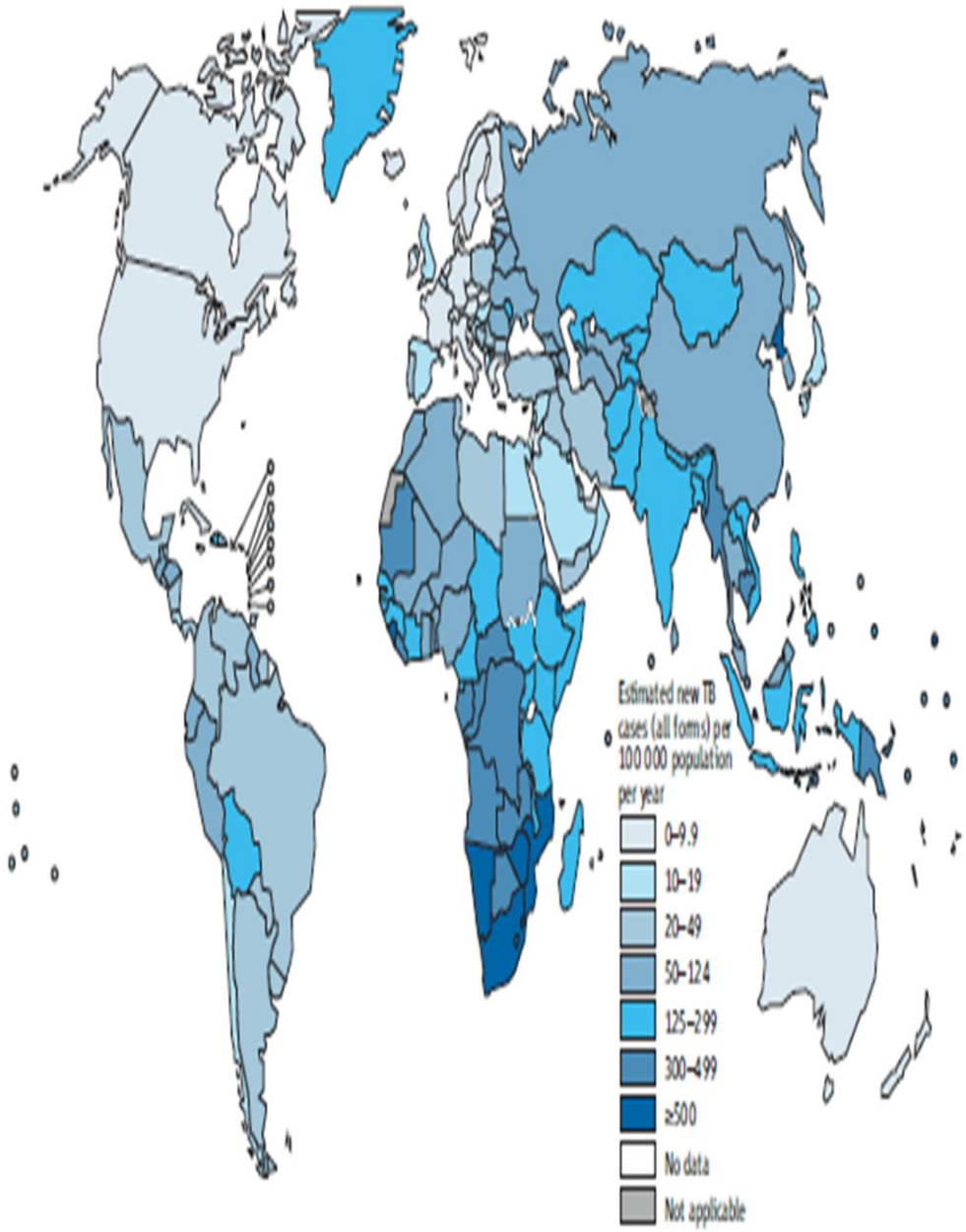
Estimated TB incidence: top-ten countries, 2012







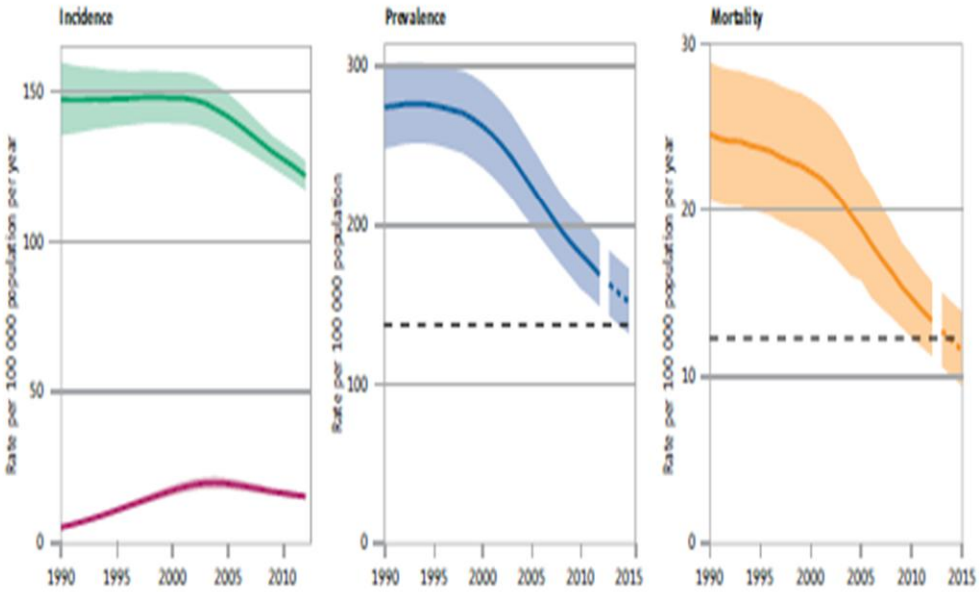
Estimated TB incidence rates, 2012



TB prevalence

In 2012 estimated prevalence TB cases were 12 million (range, 11 million–13 million). It was equivalent to 169 cases per lakhs people. The prevalence rate was fallen 37% globally from 1990 to by end of 2012[2].

Global trends in estimated rates of TB incidence, prevalence and mortality. Left: Global trends in estimated incidence rate including HIV-positive TB (green) and estimated incidence rate of HIV-positive TB (red). Centre and right: Trends in estimated TB prevalence and mortality rates 1990–2012 and forecast TB prevalence and mortality rates 2013–2015. The horizontal dashed lines represent the Stop TB Partnership targets of a 50% reduction in prevalence and mortality rates by 2015 compared with 1990. Shaded areas represent uncertainty bands. Mortality excludes TB deaths among HIV-positive people.



TB mortality

In 2012, TB deaths were an estimated 1.3 million, 9.4 lakhs deaths occurred in HIV-negative people and 3.2 lakhs deaths occurred in HIV-positive people (TB deaths occurred in HIV-positive patients were classified as HIV deaths inICD-10). These deaths included 4.1lakhs occurred in women and 74,000 occurred in children. There were deaths from MDR-TB include approximately 170 000.

In total TB deaths, approximately 75% occurred in the South-East Asia and African Regions in 2012. One-third of global TB deaths occurred in India and South Africa.

Globally in 2012 the number of TB deaths per 100 000 population averaged 13 and 17.6 when TB deaths among HIV-positive patients were included[2].

Tuberculosis disease burden in India[3]

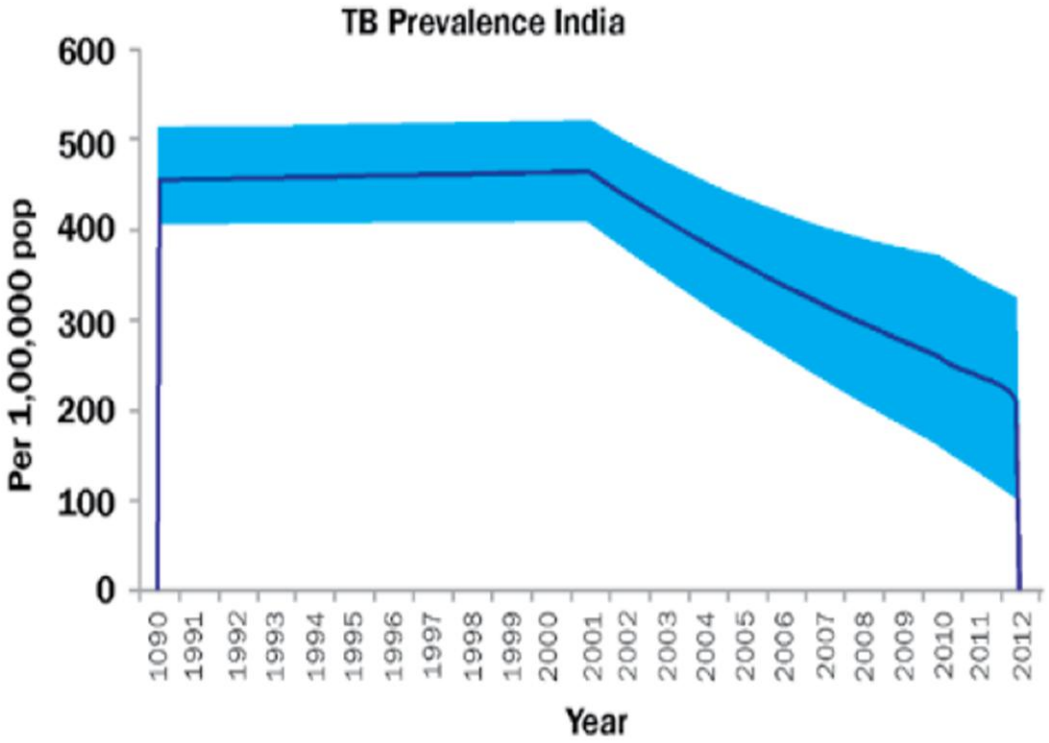
In the world India is the second most population country. Annually one fourth of the global incidence TB cases occurred in India. Globally, annual incidence of TB cases estimated about 8.6 million by the end of 2012. In which 2.3 million TB cases estimated to have occurred in India.

WHO estimated burden of tuberculosis in India, 2012

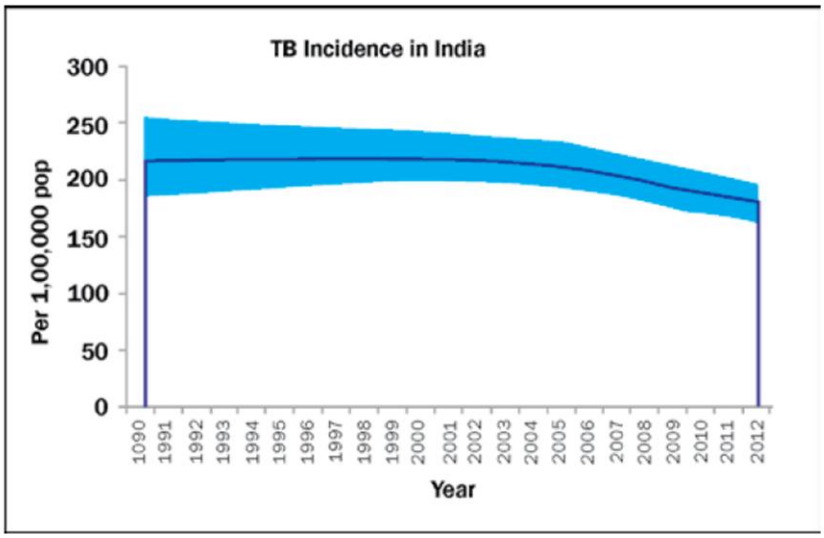
TB burden	Number (Millions) (95% CI)	Rate Per 100,000 Persons (95% CI)
Incidence	2.2 (2.0–2.4)	176 (159–193)
Prevalence	2.8 (1.9–3.9)	230 (155–319)
Mortality	0.27 (0.17–0.39)	22 (14–32)

TB burden	Number (Millions) (95% CI)	Percent (95% CI)
HIV among estimated incident TB patients	0.13 (0.12–0.14)	5.6 (5.4-6.2)
MDR-TB among notified pulmonary TB patients	0.064 (0.049–0.079)	
MDR-TB among notified New pulmonary TB patients	0.021 (0.018–0.025)	2.2% (1.9–2.6%)
MDR-TB among notified Re-treatment pulmonary TB patients	0.043 (0.033–0.054)	15% (11–19%)

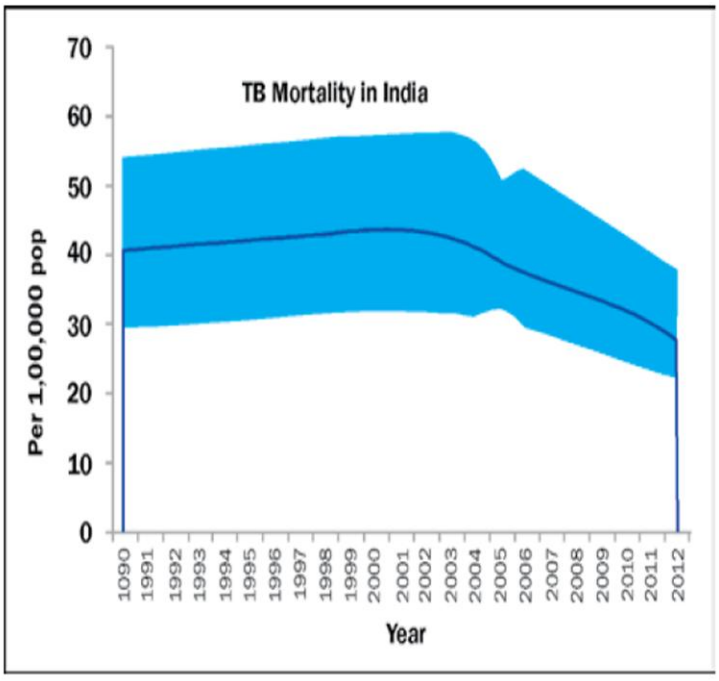
Due to TB control programme, disease burden was reduced in India. Compared to 1990, TB mortality rate reduced by 42% in 2012. Similarly compared to 1990, TB prevalence rate reduced by 51% in 2012. Tuberculosis prevalence per 100000 populations has reduced to 230 in 2012 from 465 in year 1990. In exact numbers, prevalence has reduced from 40, 00,000 to 28, 00,000 annually[3].



Tuberculosis incidence per lakh population has reduced from 216 in year 1990 to 176 in 2012.



Tuberculosis mortality per lakh population has reduced from 38 in year 1990 to 22 in 2012. In absolute numbers, morality due to TB has reduced from 3.3 lakhs to 2.7 lakhs annually.



In the above varies articles, high burden country like India, indentify the patients with active pulmonary tuberculosis is important component of TB control programme.

Pulmonary tuberculosis, most commonly diagnosed by sputum smear examination. Sputum microscopy is a low cost, high specificity test. It is essential component of the DOTS strategy of the WHO.

But not all patients with clinical picture of tuberculosis revealed acid fast bacilli in their sputum. In 22% to 61% of the patients smear negative – culture positive were observed[4-6].

Sputum smear negative pulmonary tuberculosis still remains common problem, particularly in retreatment patients, faced by clinician.

They continuous source of infection to the community if their delay in diagnosis and treatment of these patients.

In our study we used the fibre optic bronchoscopy as a primary tool for diagnosis of smear negative retreatment pulmonary tuberculosis and early treatment renders those patients non infectious, interrupts the transmission of TB and reduce the incidence of MDR-TB in those patients.

REVIEW OF LITERATURE

Mycobacterium tuberculosis

Koch (1882) isolated the mammalian tubercle and revealed its causative role in tuberculosis by Koch's postulates. The generic name mycobacterium was introduced by Lehmann and Neumann.

Morphology

The bacilli are straight, slender or slightly curved rod shaped organism.

Two to four micrometer in length and 0.2 to 0.8 micron in breadth. Presents singly, in pairs or in small groups.The bacilli are non-sporing, non-motile, and non-capsulated.

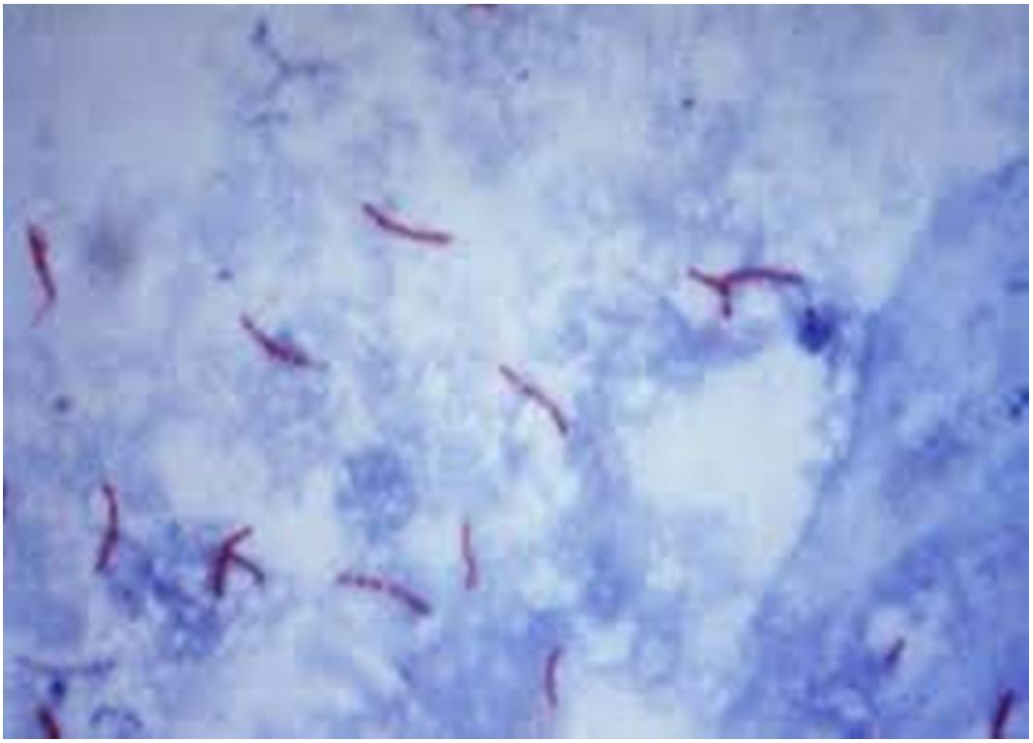
The bacilli are gram positive. They do not take the stains readily. These organisms resist decolourization by 25% H_2SO_4 and absolute alcohol for 10 minutes, so these are called acid fast and alcohol fast. Acid fastness is based on integrity of cell wall[7].

Mycobacterium cell wall

It has high lipid content. It is accounts for about 60% of the cell wall weight.

The cell wall has several distinct layers. Inner layer-overlying the cell membrane is composed of peptidoglycan (murein).

External layer-which is external to murein, called as arabinogalactan, which is covalently linked to mycolic acid.



Susceptibility to physical and chemical agents

The thermal death time at 60 degree Celsius is 15 min to 20 min. They are more resistant to chemical agents.

This organism can survive exposure to five per cent phenol, four percent sodium hydroxide, fifteen per cent sulphuric acid.

The culture of tubercle bacilli can be killed by exposure to sunlight there hours.

Tubercular bacilli can survive for 20 to 30 hours in sputum. In droplets may survive for 8 to 10 days. The organism can survive for long periods in dried sputum[7].

Antigenic structure

1) Soluble [cytoplasmic] and insoluble[cell wall lipid bound]

2) Carbohydrate or proteins.

Polysaccharides are responsible for group specificity. Type specificity is due to protein antigen. Following infection, delayed hyper sensitivity reaction develops to protein (tuberculin).

Pathogenesis

The source of infection is mostly an open case of pulmonary tuberculosis.

The mode of infection is direct inhalation of aerosolized bacilli in droplet of expectorated sputum. Coughing release numerous droplets- as many as 3000 infectious nuclei per cough.

Spread occurs often among household and prolonged contacts of open cases.

The majority of inhaled bacilli are arrested at upper respiratory tract by natural defense mechanism. Alveolar

macrophages ingested the tubercle bacilli when in it reaching the alveoli.

Outcome of the infection was influenced by several factors including number of bacilli, virulence of the bacilli, genetic susceptibility, age, immunocompetence, stress, nutrition & coexisting illness.

Mycobacterium tuberculosis does not secrete any toxin. The exact mechanism of their virulence is not understood, suggesting their ability to survive and multiply in macrophages.

The only specific immunity effective against tuberculosis was cell mediated immunity. Humoral immunity was not much important in tuberculosis.

The important cell is the activated CD4+ helper T cell. It develops along two different paths-the Th-1 & Th-2cells. These cells release interferon r (gamma), TNF alpha, IL-1, IL-2, IL-4, IL-5, IL-10[8].

Th-1 dependent cytokines activate macrophages induce protective immunity & contain the infection. Th-2 cytokines induce delayed type hypersensitivity and tissue destruction.

The essential pathology in tuberculosis was the formation of the tubercle lesion in infected tissues. This is called as granuloma, composed of peripheral zone of lymphocytes, fibroblasts, central zone of giant cells, with or without caseation.

Tuberculous granuloma is primarily of two types,

i) Hard granuloma

ii) Soft granuloma

Hard granuloma:

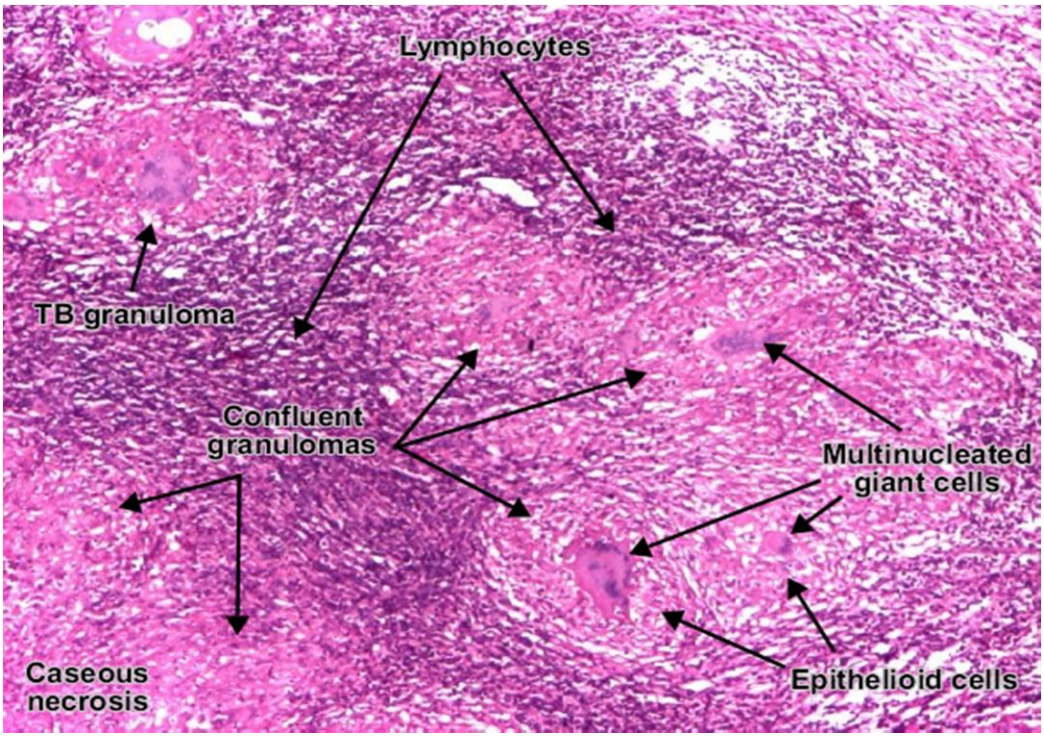
Hard granulomas are well circumscribed with a lymphocyte cuff surrounding well-aggregated epitheliod histocytes. Plasma cells and neutrophils are scant. Surrounding fibroblast proliferation is more marked. These lesions also

called Proliferative lesions and are less likely contain AFB bacilli.

Soft granuloma:

Soft granuloms are less well- demarcated, comprise of lymphocytes, macrophages, neutrophils and epitheloid histocytes arranged in a loose collection with little fibroblastic proliferation. These lesions also called exudative lesions and are likely contain AFB.

Histopathology image of tuberculous granuloma



Tuberculosis infection may be classified as primary and post primary depending upon the time of infection and the type of response.

Primary pulmonary tuberculosis

Primary tuberculosis is the initial infection by tuberculous bacilli, this usually occurs in young children. The bacilli engulfed by alveolar macrophages multiply, causing sub pleural focus of tuberculous lesion. It located in upper part of lower lobe, or lower part of middle lobe on right side (Ghon focus). Hilar nodes are involved.

Ghon focus together with the enlarged hilar node is called primary complex.

In the majority of patients the lesion heals spontaneously, leaving behind a calcified nodule, but a few bacilli may survive in the healed lesion causing latent infection.

In a few, particularly in children with impaired immunity, the primary lesion may enlarge, producing progressive primary tuberculosis.

Post primary tuberculosis

It is due to exogenous reinfection or reactivation of the latent infection. It affects mainly the upper lobe, the lesion undergoing necrosis and cavitation. Lymph node involvement is unusual. In the immunodeficient, cavity formation is unusual. Instead there is extensive dissemination of lesions in the lungs and other organs.

Conditions predisposing to the development of tuberculosis

- Immunodeficiency disorders affecting CMI including HIV infection and AIDS
- Poorly controlled diabetes mellitus
- Immunosuppressive therapy

- Immunomodulater drugs (e.g. infliximab, etanercept)
- Malignant neoplasm, organ transplantation
- Silicosis, chronic renal failure, haemodialysis
- High dose, long-term corticosteroid treatment
- Decompensated liver disease

Symptoms of Pulmonary Tuberculosis

- Cough with expectoration more than two weeks
- Chest pain
- Fever with evening rise of temperature
- Haemoptysis
- Weight loss and Appetite loss
- Shortness of breath
- Night sweats
- Tiredness

Diagnosis of Pulmonary Tuberculosis

A pulmonary tuberculosis suspect [9]

- A person with cough 2 weeks or more
- Contacts of sputum-positive tuberculosis cases, who is having cough of any duration
- Suspected/confirmed extra-pulmonary tuberculosis who is having cough of any duration
- PLHA patient, who is having cough of any duration

Direct demonstration of mycobacterium by staining method

Sputum smear examination by microscopy: at least 10000 bacilli per ml of sputum is required for positive results. Ziehl-neelsen technique is most commonly used.

Grades according to the number of bacilli seen with ziehl-neelsen staining

If the slide has:	No. of fields to be examined	Grading	Result
No AFB in 100 oil immersion fields	100	0	Neg
1-9 AFB per 100 oil immersion fields	100	Scanty*	Pos
10-99 AFB per 100 oil immersion fields	100	1+	Pos
1-10 AFB per oil immersion field	50	2+	Pos
More than 10 AFB per oil immersion field	20	3+	Pos

*Record actual number of bacilli seen in 100 fields - e.g. "Scanty 4"

Other staining methods

Cold staining methods (kinyoun"s or with gabett"s solution)

Fluorescent staining using

- Auramine-o
- Auramine-rhodamine
- Rhodamine
- Acridine orange

X-ray chest

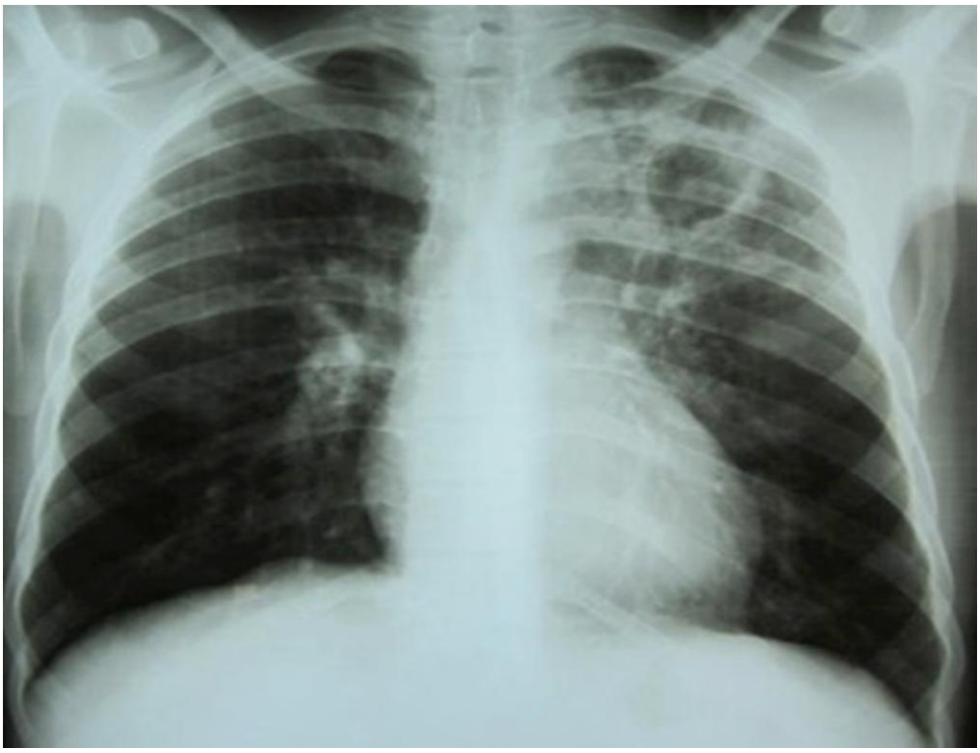
Demerits of X-ray chest:

 High intra and inter- reader variation

 In X ray no features (lesions) is characteristic of Tuberculosis

 10–15% culture-positive patients remain undiagnosed (under reading)

 40% cases diagnosed as TB by X-ray alone really do not had active Tuberculosis (over reading).



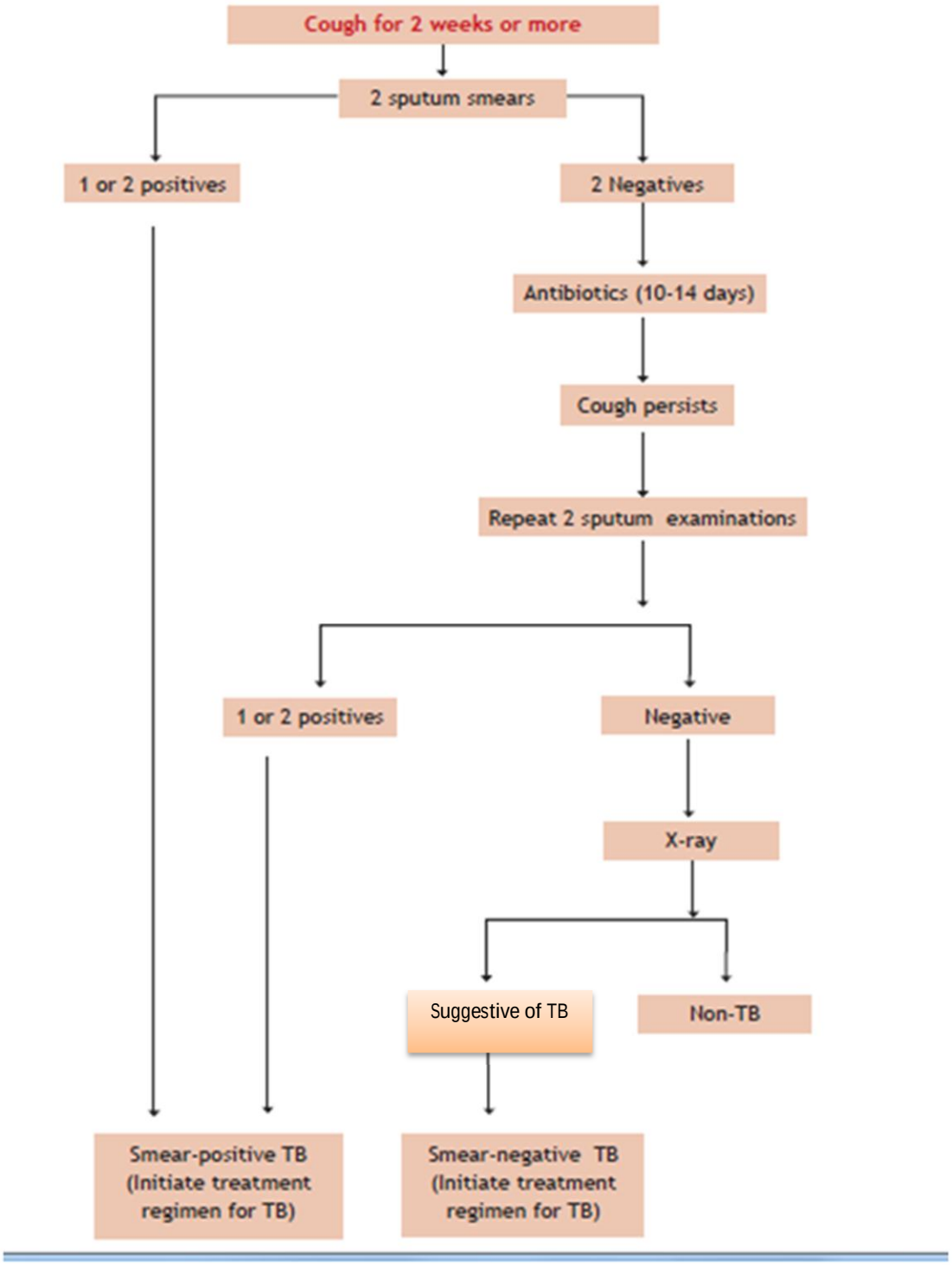
Chest X ray shows left upper lobe cavity

This chest X ray posterior anterior view shows left upper zone cavity with heterogeneous opacity, features suggestive of tuberculosis.

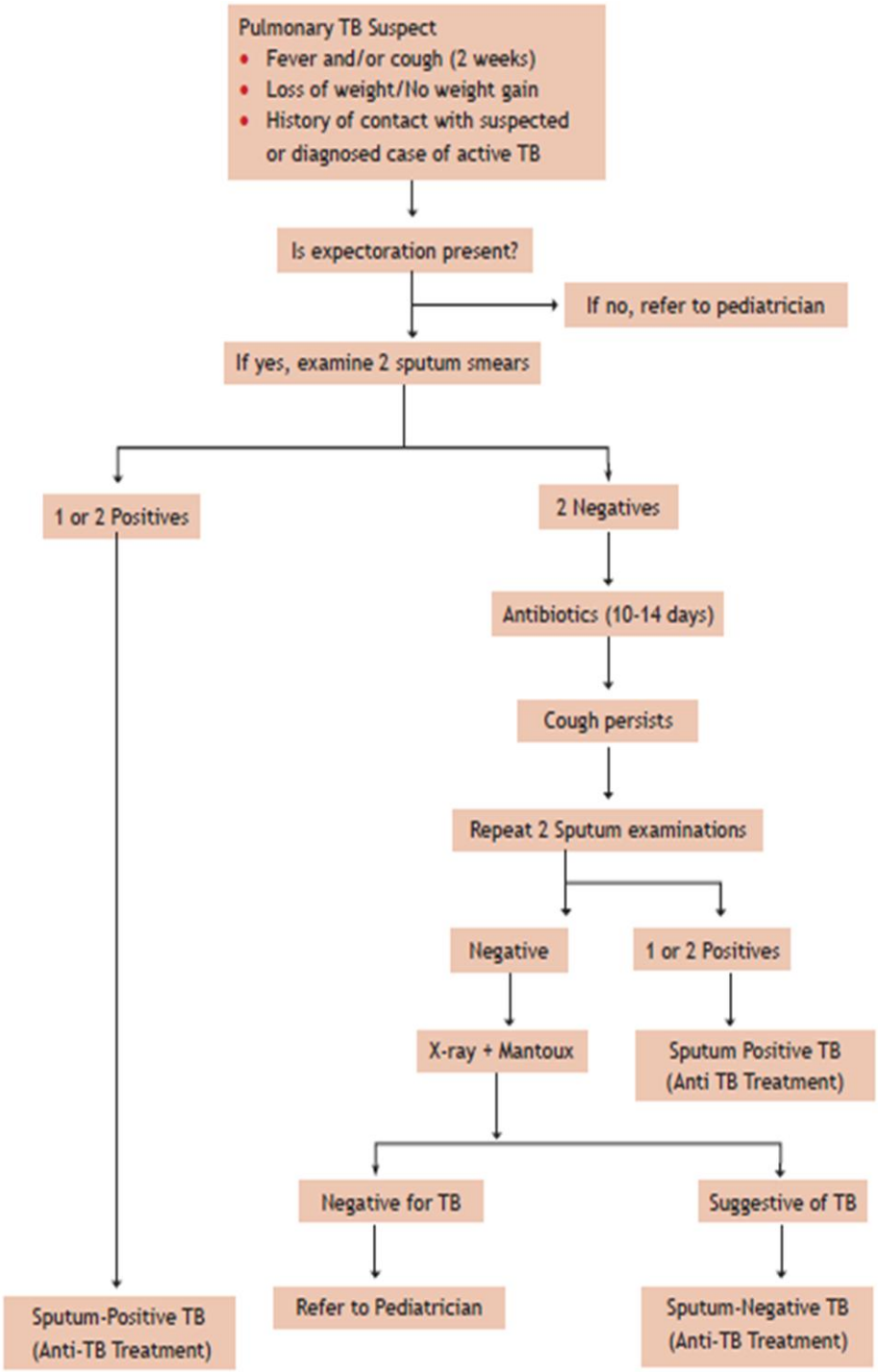
But it is not a pathagnomic and characteristic features of tuberculosis.

It is only confirmed by sputum smear examination.

Diagnostic algorithm for pulmonary tuberculosis[9]



Diagnostic algorithm for pediatric pulmonary tuberculosis



Isolation of Mycobacteria by Culture

Culture methods provide definitive diagnosis of mycobacterium by identity of the organisms and establishing the viability.

The culture method is considered gold standard, it can detect as few as 10 to 100 bacilli per ml.

Culture characters

The growth appears in about two weeks but can be delayed up to six to eight weeks. Optimum PH for growth is 6.4 to7.0. Optimum temperature is 37^0 C. increased CO_2 tension (5% to 10%) enhances the growth[7].

Culture media

Solid media

Lowenstein – Jensen

Loeffler serum slope

Pawlowskys potato medium

Tarshis medium (blood medium)

Liquid Media

Dubos medium

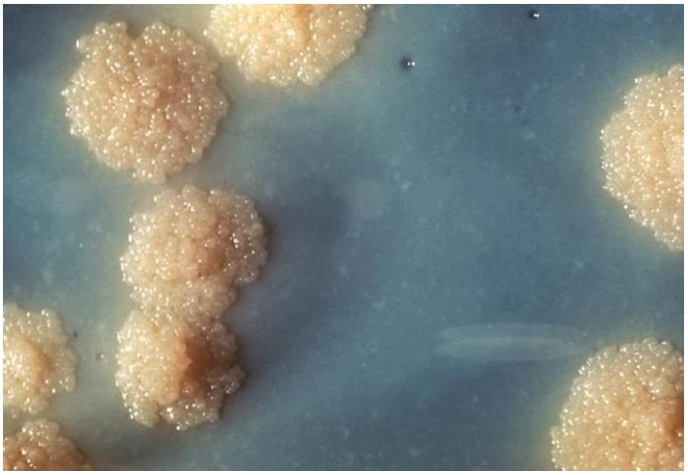
Middle brook's medium

Sula's medium

Sauton's medium

Colony characteristics

On solid media human type of tubercle bacilli give rise to following character. It is discrete, raised, irregular, dry, wrinkled colonies. They are creamy white in the beginning, then develop buff colour.



M.bacilli growth on solid media

Rapid culture methods

1) BACTEC radiometric system

2) Septi chek acid-fast bacilli method

It is a biphasic – culture approach for detection and isolation of mycobacterium tuberculosis

3) Rapid liquid tuberculosis culture

Also known as Mycobacteria Growth Indicator tube (MGIT)

4) Mycobacteriophage-based detection tests

Phage-based tests require limited culture facilities, it will give rapid results (within 2 days)

Tests for confirmation of identity

Biochemical properties of tuberculous bacilli

i) Production of niacin positive

ii) Binding to neutral test positive

iii) Nitrate reduction test positive

iv) Nicotinamidase and pyrazinamidase activity positive

v) Susceptibility to pyrazinamide positive

Immunodiagnosis

- Antibody detection test

Immunoglobulin I_gG and I_gM detection against A60 antigen most commonly used.

- Antigen detection test

Lipoarabinomannan urine test

Flow-through filter test

- Polymerase chain reaction sequencing

This test is used for detection of rifampicin resistance

- Identification of mycobacterium by high performance liquid chromatography

- ❑ Gas – liquid chromatography
- ❑ Cepheid GeneXpert

Completely closed automated system using real-time PCR. It detects the rifampicin resistance.

- ❑ Drug susceptibility testing
- ❑ Microscopic –observation drug-susceptibility assay

TREATMENT[9]

Table shows treatment regimen and type of patient

Treatment groups	Type of patient	Regimen[1]	
		Intensive Phase (IP)	Continuation Phase (CP)
New*	Sputum smear-positive Sputum smear-negative Extra-pulmonary Others	$2H_3R_3Z_3E_3$	$4H_3R_3$
Previously Treated**	Smear-positive relapse Smear-positive failure Smear-positive treatment after default Others[2]	$2H_3R_3Z_3E_3S_3$ / $1H_3R_3Z_3E_3$	$5H_3R_3E_3$

Patients weight >60kg, need additional 150 mg of rifampicin.

Patients age > 50yrs received 500mg streptomycin.

Treatment of pediatric tuberculosis

Pediatric PWB with Dosages

Drugs	Product code (PC) -13		Product code (PC) -14		PC-15	PC-16
	IP 24 blisters	CP 18 blisters	IP 24 blisters	CP 18 blisters	12 blisters	12 blisters
Isoniazid	75 mg	75 mg	150 mg	150 mg	Prolongation of IP for PC 13	Prolongation of IP for PC 14
Rifampicin	75 mg	75 mg	150 mg	150 mg		
Pyrazinamide	250 mg		500 mg			
Ethambutol	200 mg		400 mg			

Pediatric patient wise boxes for new cases according to weight band

Weight band	For New cases		Prolongation of IP
	IP	CP	
6-10 Kg	PC 13		PC 15
11-17 Kg	PC 14		PC 16
18-25 Kg	PC 13 + PC 14		PC 15 + PC 16
26-30 Kg*	PC 14 + PC 14		PC 16 + PC 16

* For children weighing >30 kgs, adult PWB are to be used

** For patients falling in b/w weight bands should be put on lower wt band

Pediatric patient wise boxes for previously treated cases according to weight band

Weight	For previously treated cases		Prolongation of IP
	IP	CP	
6-10 Kg	(PC 13+ PC 15) + (24 vials Inj. SM *)	(PC 13 + 54 Tab E 200 mg) + (PC 15 without Z)	PC 15
11-17 Kg	(PC 14 + PC 16) + (24 vials Inj. SM *)	(PC 14 + 54 E 400 mg) + (PC 16 without Z)	PC 16
18-25 Kg	(PC 13 + PC 14 + PC 15 + PC 16) + (24 vials Inj. SM *)	(PC 13 + PC 14 + 54 Tab E 600 mg) + (PC 15+ PC 16 without Z)	PC 15 + PC 16
26-30 kg	(PC 14 x 2)+ (PC 16 x 2) + (24 vials Inj. SM*)	(PC 14 x 2+ 54 Tab E 800 mg) + (2 x PC 16 without Z)	PC 16 x 2

* Injection streptomycin 15mg/Kg body weight

Multi-Drug Resistant Tuberculosis

Mycobacterium tuberculosis resistance to Rifampicin and Isoniazid with or without resistance to other first line drugs.

Data from studies, MDR-TB levels of 1% to 3% in new cases and approximately 12% in previously treated cases[10,11].

Regimen for MDR-TB

In this regimen 6-9 months of the Intensive Phase comprises of 6 drugs - Kanamycin, Levofloxacin, Pyrazinamide, ethionamide, Ethambutol and Cycloserine and in 18 months of the Continuation Phase comprises 4 drugs Levofloxacin, Ethionamide, Ethambutol and Cycloserine.

Table 7.2: Regimen for MDR TB dosage and weight band recommendations

S.No	Drugs	16-25 Kgs	26-45 Kgs	46-70 Kgs
1	Kanamycin	500 mg	500 mg	750 mg
2	Levofloxacin	250 mg	750 mg	1000 mg
3	Ethionamide	375 mg	500 mg	750 mg
4	Ethambutol	400 mg	800 mg	1200 mg
5	Pyrazinamide	500 mg	1250 mg	1500 mg
6	Cycloserine	250 mg	500 mg	750 mg
7	Pyridoxine	50 mg	100mg	100mg
	Na-PAS (80% weight/vol)[2]	5 gm	10 gm	12 gm
	Moxifloxacin (Mfx)	200 mg	400 mg	400 mg
	Capreomycin (Cm)	500 mg	750 mg	1000 mg

Patients weighing < 16 kg and > 70 kg may require different dosage of the drugs in the MDR TB regimen.

Table 7.4: Dosage of Regimen for MDR TB for paediatric age group <16 kg

Drug	Daily Dose – mg/kg body weight
Kanamycin / Capreomycin	15-20 mg/kg
Levofloxacin / Moxifloxacin	7.5-10 mg/kg
Ethionamide	15-20 mg/kg
Cycloserine	15-20 mg/kg
Ethambutol	25 mg/kg
Pyrazinamide	30-40 mg/kg
(Na-PAS)	150 mg/kg

In patients weighing > 70 kg,

Kanamycin/Capreomycin (1 gm), cycloserin(1gm), Ethionamide (1gm), Pyrazinamide (2 gm) and Ethambutol (1.6gm). Other drugs dosages would remain the same.

Extensively Drug-Resistant Tuberculosis (XDR-TB)

XDR-TB is defined as Mycobacterium tuberculosis resistance to rifampicin, isoniazid, one of the fluroquinolones, and at least one of the second line injectable drugs like kanamycin, capreomycin, amikacin.

Treatment for XDR-TB

Intensive Phase consists of 7 drugs - Capreomycin (Cm), PAS, Moxifloxacin (Mfx), High dose-INH, Linezolid, Clofazimine, and Amoxyclav. Duration of IP was 6 to 12 months.

Continuation Phase consists of 6 drugs – PAS, Moxifloxacin (Mfx), High dose-INH, Linezolid, and Amoxyclav, clofazimine. Duration of CP was 18 months

Regimen for XDR TB dosage and weight band recommendations

Drugs	Dosage/day	
	≤ 45 Kgs	> 45 Kgs
Inj. Capreomycin (Cm)	750 mg	1000 mg
PAS	10 gm	12 gm
Moxifloxacin (Mfx)	400 mg	400 mg
High dose INH (High dose-H)	600 mg	900 mg
Clofazimine (Cfz)	200 mg	200 mg
Linezolid (Lzd)	600 mg	600 mg
Amoxyclav(Amx/Clv)	875/125 mg BD	875/125 mg BD
Pyridoxine	100 mg	100 mg
Reserve/Substitute drugs		
Clarithromycin (Clr)	500 mg BD	500 mg BD
Thiacetazone (Thz)#	150 mg	150 mg

Depending on availability, not to be given to HIV positive cases

Treatment of HIV and TB co-infection[12]

ART in patients with active TB

If patient with active TB is diagnosed with HIV who requires ART, first to start anti-tuberculosis treatment. ART may need to be started later.

Initiation of ART in relation to anti-TB therapy

CD4 cell count (cells/mm3)	Timing of ART in relation to initiation of TB treatment	ART recommendations
CD4 count of any value	Start ATT first Start ART as soon as TB treatment is tolerated (between 2 weeks and 2 months)	Recommend ART EFV-containing regimens
Rationale for ART recommendation during TB treatment (References 6,7,8,9,10,11) : In the absence of ART, TB therapy alone does not significantly increase the CD4 cell count. Nor does it significantly decrease the HIV viral load. Thus, CD4 counts measured during active TB are likely to reflect the actual level of immunosuppression The use of HAART in patients with TB can lead to a sustained reduction in the HIV viral load. It can also facilitate immunological reconstitution, and decrease AIDS-defining illness and mortality. This benefit is seen across different ranges of CD4 counts		

If TB was diagnosed in patient who was already on ART

First-line or second-line ART regimen	ART regimen at the time TB occurs	Management options
First-line ART	(AZT or TDF) + 3TC + EFV	Continue with two NRTIs + EFV
	(AZT or TDF)+ 3TC + NVP	Substitute NVP with EFV(i),(ii)
Second-line ART	Two NRTIs + PI	Substitute Rifampicin with Rifabutin in the ATT
Notes: i) Shifting back to the original regimens once the rifampicin-containing regimen is completed is recommended. When substituting back from EFV to NVP, no lead-in dose is required. ii) EFV should not be used in the first trimester of pregnancy. In women of child-bearing age, the use of contraceptives should be ascertained.		

AZT- Zidovudine; TDF- Tenofavir; EFV- Efavirenz;

3TC- Lamivudine; NVP- Nevirapine

NRTIS-Nucleoside reverse transcriptase inhibitors

PI-Protease inhibitors

Common side effects of first – line anti-tuberculosis drugs[13]

Isoniazid

Skin rash

Hepatitis

Lethargy and Sleepiness

Peripheral neuropathy

Rifampicin

Abdominal pain, nausea, vomiting

Thrombocytopenic purpura

Cutaneous reaction

Hepatitis

Flu like syndrome on intermittent dosage

Ethambutol

The main adverse effect is retro bulbar neuritis

Streptomycin

Renal damage

Vestibular and auditory nerve damage

Cutaneous hypersensitivity

Pyrazinamide

Hepatitis

Arthralgia

Most common adverse drug reaction to second line ATT drugs[14]

Injectables – Kanamycin / Capreomycin

Ototoxicity [32,33]

Vertigo

Nephrotoxicity

Electrolyte imbalance

Ethionamide

- Epigastric discomfort, anorexia, nausea, metallic taste, vomiting, excessive salivation.
- Gynaecomastia, peripheral neuropathy, menstrual disturbances, acne, impotence, and headache.
- Hypothyroidism and goiter with prolonged administration
- Hepatitis
- Psychiatric: hallucination and depression

Ofloxacin, Levofloxicin, Moxifloxacin [15,16]

- ❑ Diarrhoea, vomiting, and abdominal pain
- ❑ Tendinopathy and tendinitis
- ❑ Dizziness and convulsions
- ❑ Cardiotoxicity – QT prolongation
- ❑ Phototoxicity and photosensitivity
- ❑ Arthralgia
- ❑ Skin rash

PAS

- Anorexia, nausea, vomiting, and abdominal pain
- Hypokalemia
- Hepatic dysfunction
- Skin rash
- Hypothyroidism and goiter with prolonged administration

Cycloserine

- CNS: dizziness, slurred speech, headache, tremor, insomnia and convulsions.
- Hypersensitivity reaction
- Psychiatric: confusion, depression, suicidal tendency, and altered behavior.

Treatment outcomes[13]

Cured:

Patient whose sputum AFB smear is negative in the last month of treatment and on at least one time previous occasion during treatment.

Treatment completed:

Patient who has completed the treatment but does not meet the criteria for failure or cure.

Treatment failure:

Patient whose sputum smear is positive at 5 months or later during treatment.

Died:

Patient who dies for any reason during the course of treatment.

Defaulter:

Patient whose treatment was interrupted for 2 months or more.

Transfer out:

A patient who transferred to another unit and whose treatment outcome is not known.

Complications of pulmonary tuberculosis

Local

- Haemoptysis
- Post-tuberculosis bronchiectasis
- Aspergilloma
- Tuberculosis endobronchitis and tracheitis
- Spontaneous Pneumothorax
- Scar carcinoma
- Disseminated calcification of the lung
- Pulmonary function changes, obstructive airways disease
- Secondary pyogenic infections

Systemic

- Secondary amyloidosis
- Chronic respiratory failure
- Corpulmonale

Smear negative pulmonary tuberculosis

A patient with symptoms suggestive of TB whose two sputum smear examination is negative for AFB, with evidence of pulmonary TB by Chest X ray or microbiological method (approved molecular methods or culture positive) is classified as smear negative pulmonary tuberculosis.

Importance of detecting smear-negative tuberculosis

By using DNA finger printing in area with low transmission of tuberculosis (sanfrancisco)[17], 17% of the transmission due to smear-negative, culture positive index patients. Published data suggest that over 50% of smear negative patients would needing anti tuberculous treatment by the end of 12 months if untreated[18,19].

Data from longitudinal survey from Bangalore, India[18] shows the mortality rate of smear negative, culture positive patients was 14.1% compared with the 34.7% of smear positive cases at the end of 18 month follow up.

So the diagnosis and treatment of smear negative retreatment pulmonary tuberculosis is important.

Diagnosis of sputum AFB smear –negative pulmonary tuberculosis patients were difficult and many patients being put on anti-tubercular treatment empirically, leading many time to avoidable risk of drug toxicity, particularly retreatment cases and in smear negative retreatment cases to decide about CAT II ATT also important.

Following methods are used for diagnosis of smear negative pulmonary tuberculosis

- ❖ Induced sputum by hypertonic saline
- ❖ Gastric lavage
- ❖ Radiologically guided transthoracic needle aspiration
- ❖ Transtracheal needle aspiration
- ❖ Bronchoscopy procedures
    - o *Rigid bronchoscopy*
    - o *Flexible fibreoptic bronchoscopy*

- ❖ Bronchial brush smear
- ❖ Bronchial washings
- ❖ Bronchial aspirate
- ❖ Bronchoalveolar lavage
- ❖ Bronchial biopsy
- ❖ Transbronchial lung biopsy

Post-bronchoscopy sputum

Others

Peripheral blood examination using molecular and serological Methods.

We use the Flexible fibreoptic bronchoscopy as primary tool in this study, for diagnosis of smear negative retreatment pulmonary tuberculosis and it helps to, decide about CAT II ATT in those patients.

Flexible Fibreoptic bronchoscopy

Diagnostic methods applied to bronchoscopic

Specimens, in our study for diagnosis of tuberculosis is

Ziehl-Neelsen (Z-N) stain

Lowenstein-Jensen (L-J) culture

Cleaning and disinfection of bronchoscopy[20]

- ✓ It should done by trained staff in a dedicated room.
- ✓ Most important initial step is thorough cleaning with detergent.
- ✓ 2 % Glutaraldehyde is commonly used for disinfection. Bronchoscope immersed for 20 min in 2% glutaraldehyde at beginning and between the patients and end of sessions.
- ✓ Immersion times may need 60 minutes in case of HIV patients with respiratory symptoms and known or suspected case of Atypical Mycobacterium.
- ✓ Automated washer and disinfector are recommended to minimize staff contact with disinfectants and their fumes.
- ✓ Sterile or bacterial free water is used for flashing bronchoscopes. Filtered water (using 0.2 micrometer filter) or autoclave may be used.

- ✓ All rinse water pathways must be accessible for regular, preferably sessional, cleaning and disinfection.

Contraindications of bronchoscopy[21]

Absolute

- Lack of consent from the patients
- If an emergency, lack of adequate facilities, personnel to care of the patients.
- Lack of an experienced bronchoscopist to perform procedure
- In ability to adequately oxygenate the patient during bronchoscopy

Relative contraindications

- Severe obstructive air ways disease
- Severe refractory hypoxemia
- Coagulopathy or bleeding diathesis that cannot be occurred
- Unstable hypo dynamic states

Complications of Fibreoptic bronchoscopy[21]

- Complications of FOB was very rare, which include
- Cross infection of patients and infection of health care workers[34,35,36]
- Hemoptysis, epistaxsis, Pneumothorax
- Medication reaction
- Arrhythmia
- Hypoxia and hypercapnia
- Increased air way resistance
- Laryngospasm
- Bradycardia
- Bronchospasm
- Localized trauma
- Hypotension , respiratory or cardiac arrest

AIM OF THE STUDY

Aim:

Role of FOB in smear negative retreatment pulmonary tuberculosis .

Objectives:

Primary:

To know the diagnostic value of FOB in diagnosis of pulmonary Tuberculosis in patient who have already taken anti tuberculosis treatment, whose sputum smear for AFB negative, but clinical and radiological features are suggestive of active tuberculosis.

Secondary:

- Comparison of FOB wash for AFB culture by LJ medium with pre FOB sputum for LPA.
- Identify the other infection early, to prevent spread of infection in community.
- Bronchial wash and bronchial brush for cytology.

MATERIALS AND METHODS

Study design: Prospective

Work plan / Timeline: December 2013 to July 2014

Study population: Patients admitted in Govt Hospital of Thoracic Medicine, Tambaram Sanatorium.

Inclusion criteria:

Patients taken anti tuberculous treatment for more than one month (include defaulter and cured patients), now clinical and radiological features suggestive of active tuberculosis but sputum for AFB smear negative.

Exclusion criteria:

1. New smear positive TB
2. Smear positive retreatment tuberculosis
3. Pts with respiratory failure
4. Patients who are not willing to participate in the study
5. Patients who are not fit for FOB

Collection of clinical samples/data

1. Recruitment of patients as per inclusion criteria

2. Thorough clinical examination

3. Symptoms duration.

4. Antituberculous treatment history.

5. Chest radiograph

6. Sputum for AFB staining, LPA

7. FOB-Bronchial wash /brush at suspected area of lesion.

Method of study

Patients with clinical and radiological suspicion of pulmonary tuberculosis with 2 sputum smears for AFB negative, who have already taken anti tubercular treatment, were evaluated.

Fitness for FOB with cbc, bleeding time, clotting time, ECG, pulse oximetry, cardiac evaluation was done.

Fit patients were subjected to FOB, bronchial wash & brush from the suspected site was done.

Samples were analyzed by following method.

- ✓ Sputum Smear for AFB (pre and post FOB),
- ✓ Bronchial wash for AFB smear and AFB culture
- ✓ Bronchial wash for non tuberculous culture and sensitivity
- ✓ Bronchial brush for AFB smears
- ✓ Bronchial wash and brush for cytology
- ✓ Pre FOB sputum for LPA (if LPA negative culture done by Solid and Liquid Media at NIRT)

Statistical analysis:

Analysis is done using SPSS software

Ethical Clearance

The various investigations and procedures that will be used in this study will be as per protocol. The identity of each patient will be kept confidential. This study will not violate medical ethics in anyway and it will help in deciding CAT II ATT in smear negative retreatment pulmonary tuberculosis**.**

OBSERVATION
&
RESULTS

In this study we evaluate the role of FOB in smear negative retreatment pulmonary tuberculosis. Patients' recruitment is done, according to inclusion criteria and the bronchial tree is visualized by FOB and wash & brush done at the suspected area of lesion. LPA (line probe assay) of pre bronchoscopy sputum given for all the patients participating in the study.

Age of study population varies between 16 years to 78 years.

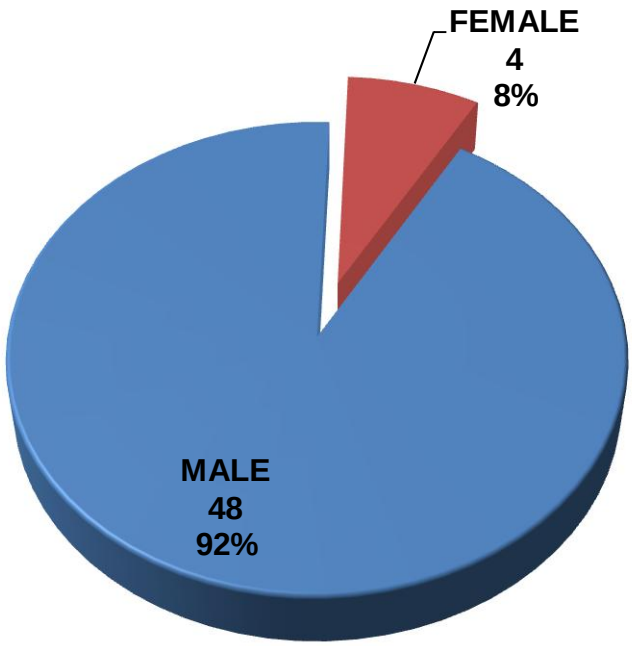
The study data analyzed and the following observation made.

In the study out of 52 patients, 4 (8%) patients female and 48 patients male (92%).

Table no: 1

GENDER	No.
MALE	48
FEMALE	4
Total	52

Chart no 1

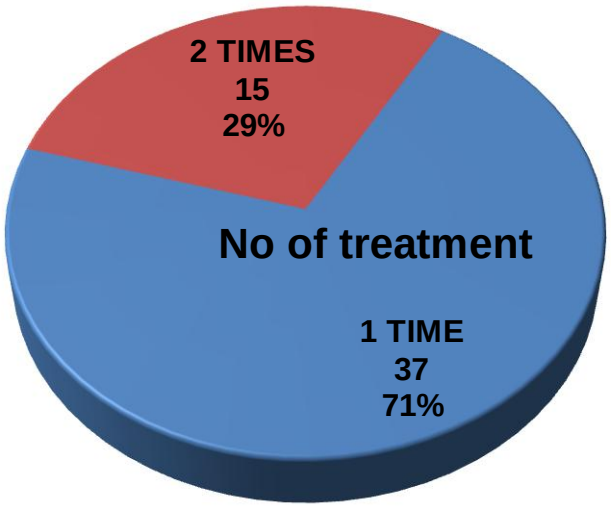


Previous history of ATT

Table no: 2

No of treatment	No.
1 TIME	37
2 TIMES	15
Total	52

Chart no: 2

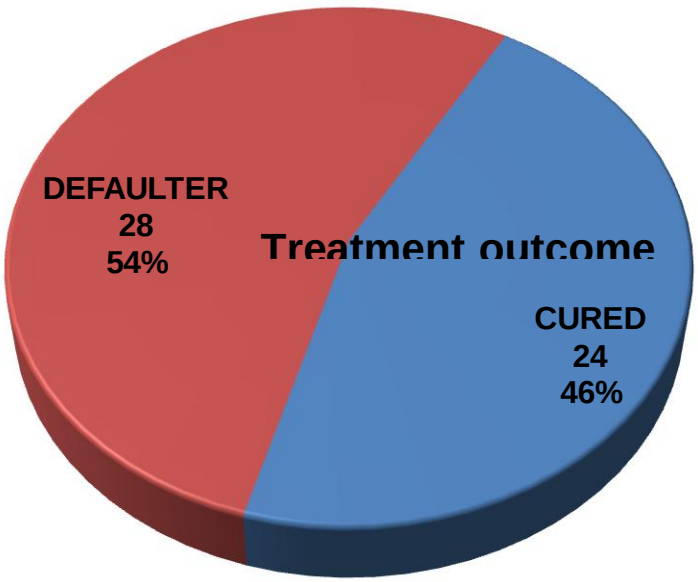


Outcome of the previous treatment

Table no: 3

Treatment outcome	No.
CURED	24
DEFAULTER	28
Total	52

Chart no: 3

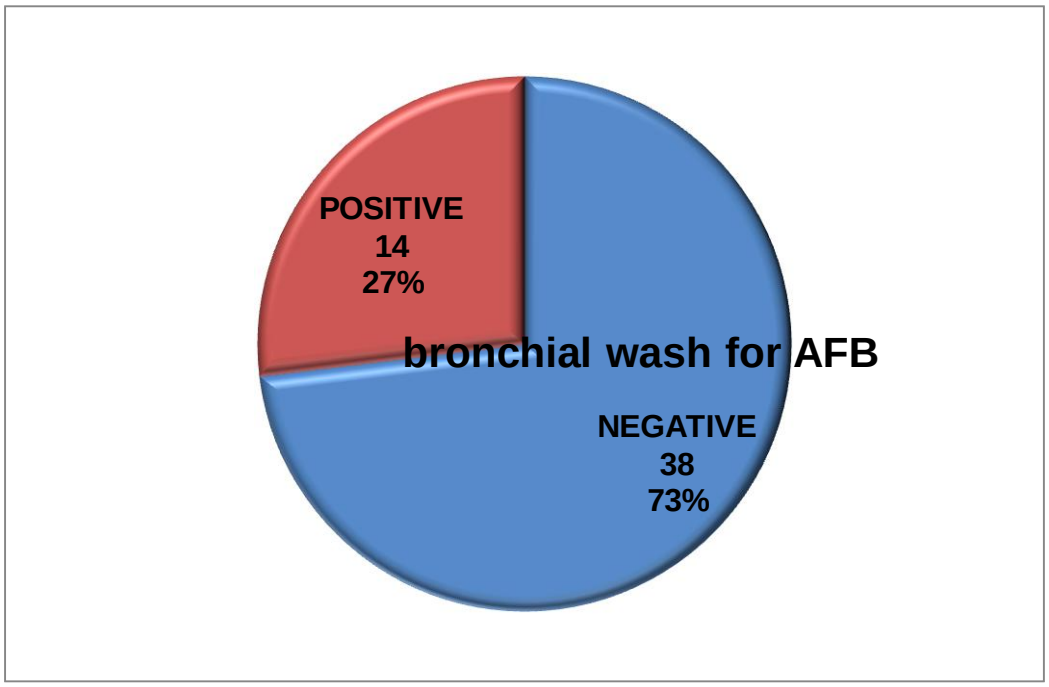


Bronchial wash for AFB smear by Ziehl-Neelsen method

Table no: 4

BRONCHIAL WASH FOR AFB	No.
NEGATIVE	38
POSITIVE	14
Total	52

Chart no: 4

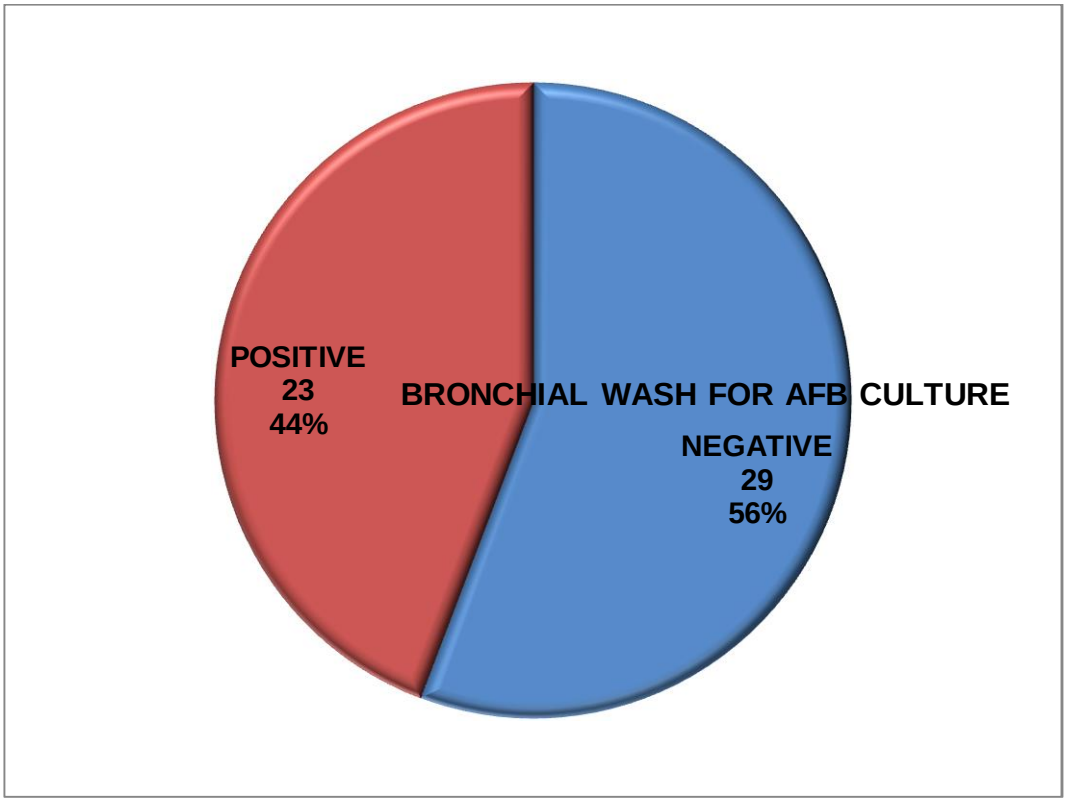


Bronchial wash for AFB culture by LJ medium

Table no: 5

BRONCHIAL WASH FOR AFB CULTURE	No.
NEGATIVE	29
POSITIVE	23
Total	52

Chart no: 5

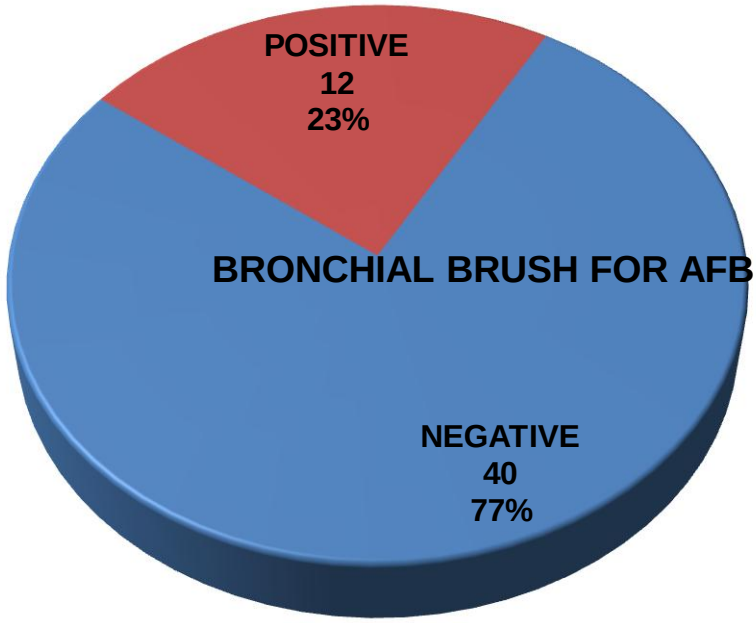


Bronchial brush for AFB smears by Ziehl-Neelsen method

Table no: 6

BRONCHIAL BRUSH FOR AFB	No.
NEGATIVE	40
POSITIVE	12
Total	52

Chart no: 6

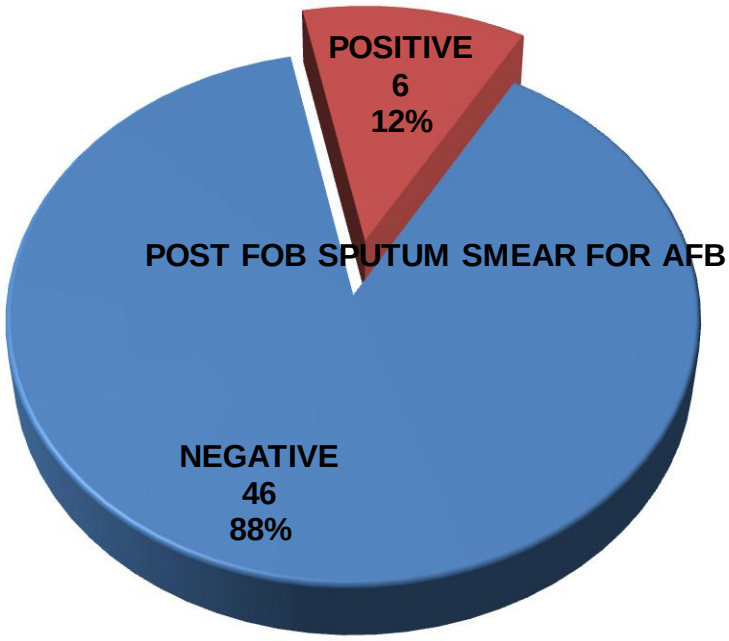


Post bronchoscopy sputum AFB smear by Ziehl-Neelsen method

Table no: 7

POST FOB SPUTUM SMEAR FOR AFB	No.
NEGATIVE	46
POSITIVE	6
Total	52

Chart no: 7

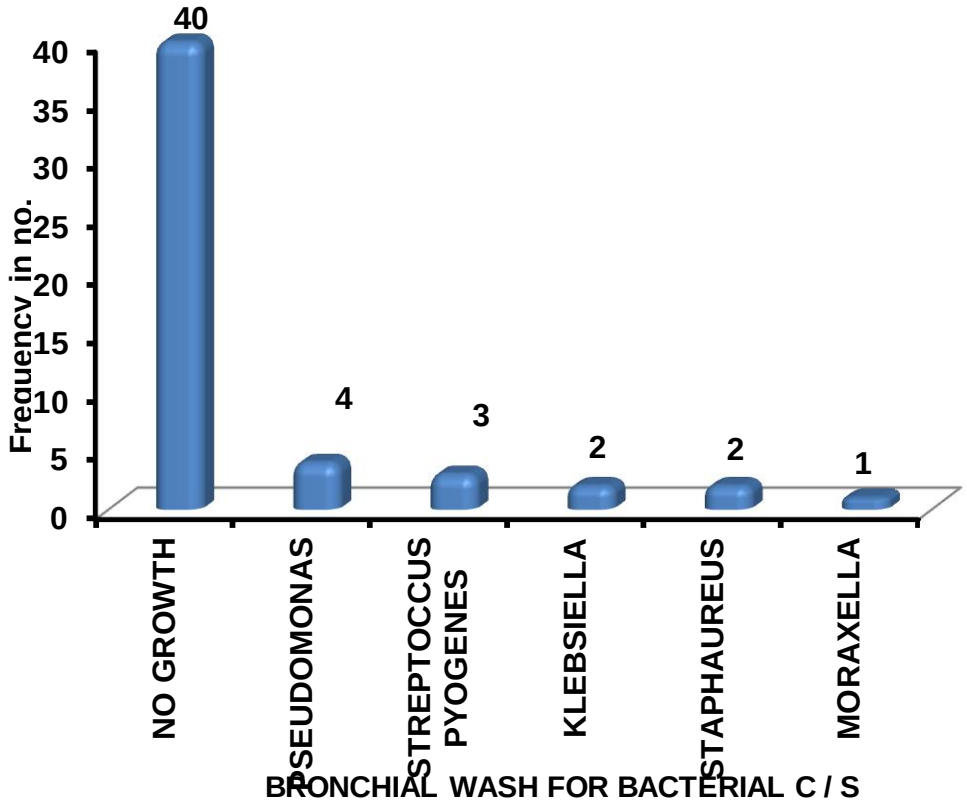


Bronchial wash for bacterial c/s

Table no: 8

BRONCHIAL WASH FOR Bacterial C / S	No.
NO GROWTH	40
PSEUDOMONAS	4
STREPTOCCUS PYOGENES	3
KLEBSIELLA	2
STAPHAUREUS	2
MORAXELLA	1
Total	52

Chart no: 8

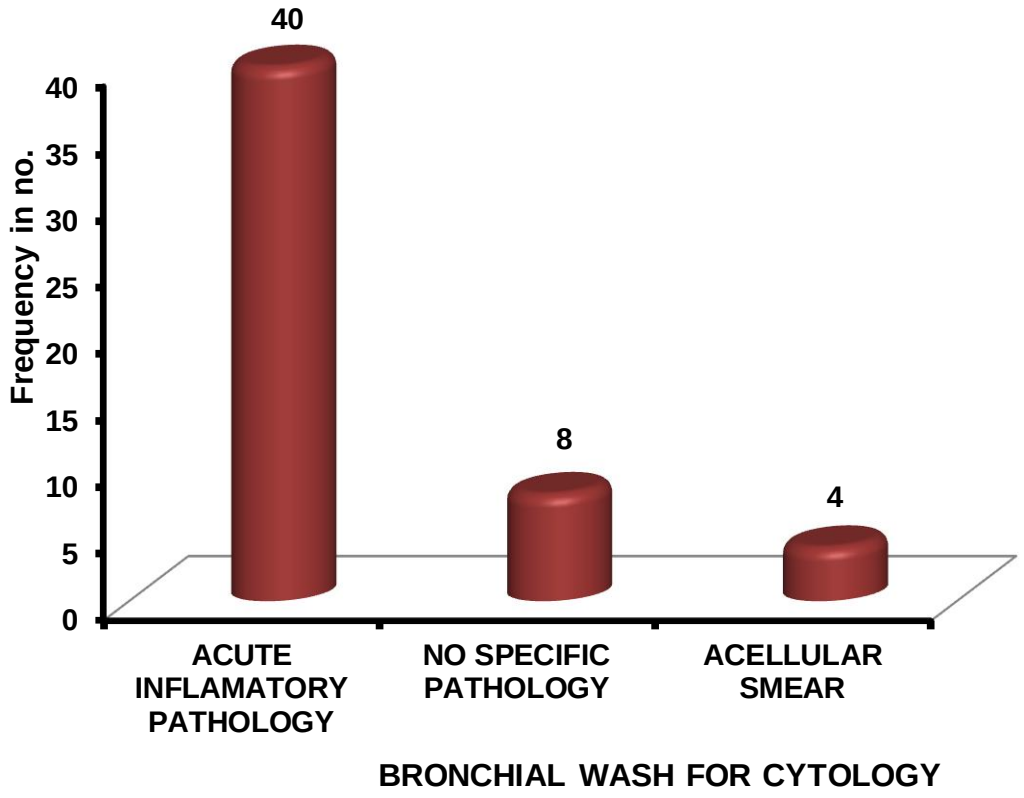


Bronchial wash for cytology

Table no: 9

BRONCHIAL WASH FOR CYTOLOGY	No.
ACUTE INFLAMATORY PATHOLOGY	40
NO SPECIFIC PATHOLOGY	8
ACELLULAR SMEAR	4
Total	52

Chart no: 9

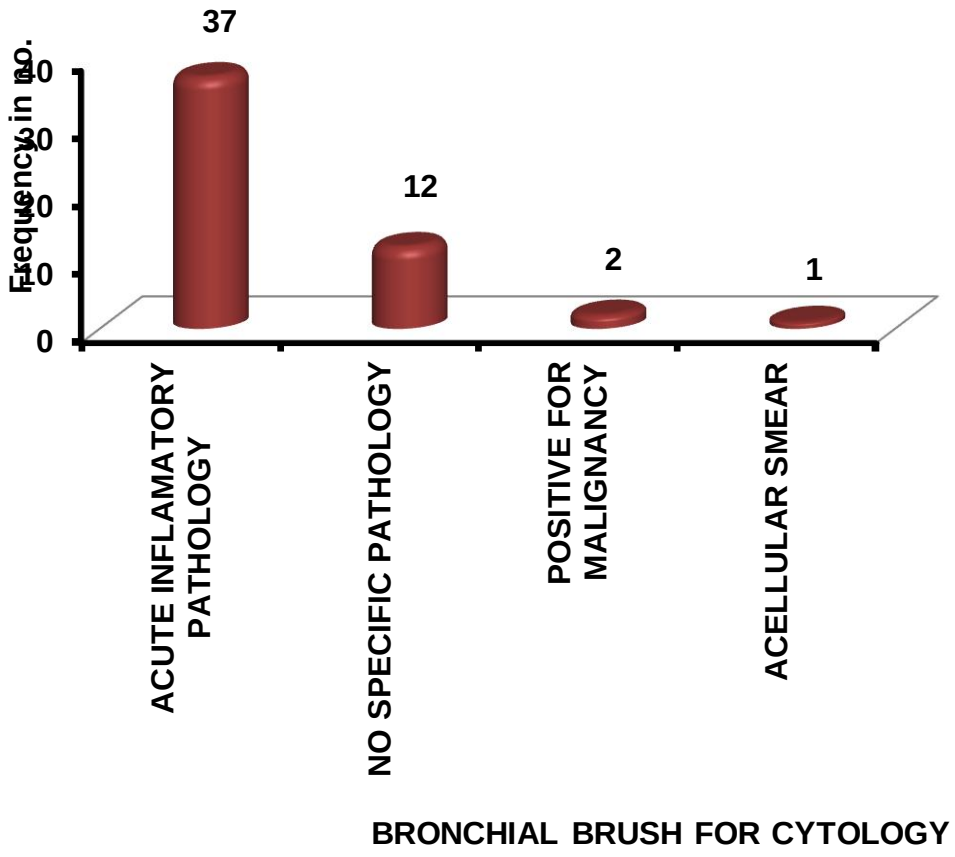


Bronchial brush for cytology

Table no: 10

BRONCHIAL BRUSH FOR CYTOLOGY	No.
ACUTE INFLAMATORY PATHOLOGY	37
NO SPECIFIC PATHOLOGY	12
POSITIVE FOR MALIGNANCY	2
ACELLULAR SMEAR	1
Total	52

Chart no: 10



Pre FOB sputum for LPA (if LPA negative, culture done by solid and liquid medium)

Table no: 11

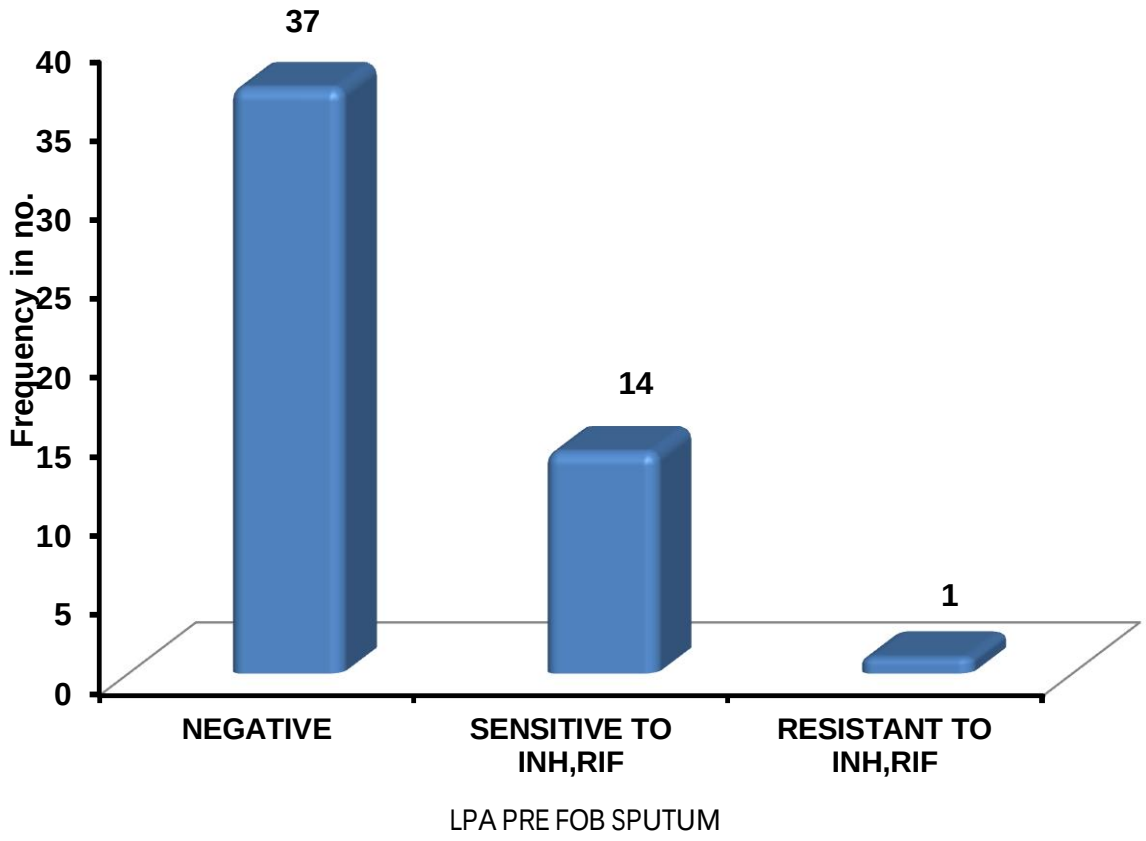
LPA PRE FOB SPUTUM	No.
NEGATIVE	37
SENSITIVE TO INH,RIF	14
RESISTANT TO INH,RIF	1
Total	52

LPA of pre bronchoscopy sputum given by all patients participate in the study

In 15 patients, mycobacterium detected, in which 5 patients LPA positive, 10 patients LPA negative but culture positive, 1 patients diagnosed as MDR TB (Resistant to INH & Rifampicin)

Pre FOB sputum for LPA (if LPA negative, culture done by solid and liquid medium)

Chart no: 11



Comparison of pre FOB sputum for LPA (include LPA Positive and culture positive) and bronchial wash AFB culture positive

Table no: 12

BRONCHIAL WASH FOR AFB CULTURE	LPA PRE FOB SPUTUM		TOTAL
	POSITIVE	NEGATIVE	
POSITIVE	14	9	23
NEGATIVE	1	28	29
TOTAL	15	37	52

Chi square p - Value <0.001

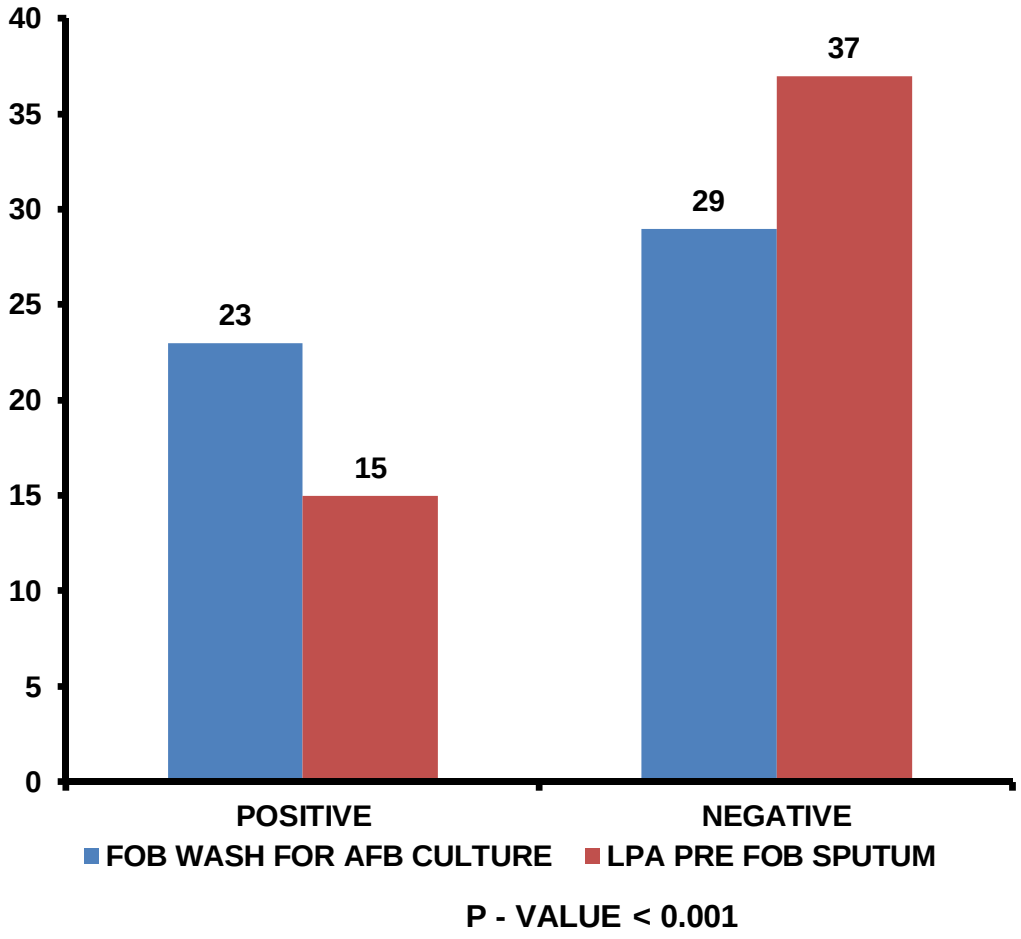
Compared to pre FOB sputum for LPA (including LPA positive, culture positive) with FOB wash for AFB culture revealed better yield (p value <0.001) in the later group.

All pre FOB sputum for LPA positive patients (including culture positive) were within the margin of FOB wash for AFB culture positive patients, except one patient whose pre FOB sputum for LPA positive but bronchial wash for AFB culture negative. That is, if FOB washes for AFB culture is negative,

LPA of pre bronchoscopy sputum is also negative (LPA negative and culture negative) (p value <0.001).

Comparison of pre FOB sputum for LPA (include LPA Positive and culture positive) and bronchial wash AFB culture positive

Chart no: 12



DISCUSSION

The WHO Expert Committee on Tuberculosis says that patients with pulmonary tuberculosis, whose disease has not been confirmed bacteriologically should be classified as suspects" untill the presence of AFB is demonstrated and a patient with persistent symptoms of tuberculosis, whose sputum does not contain AFB should be followed up and anti-tubercular treatment given only if the diagnosis confirmed by bacteriologically[22].

Published data suggest that over 50% of smear negative patients would be needing anti tuberculous treatment by the end of 12 months if untreated[23'24].

Data from longitudinal survey from Bangalore, India shows the mortality rate of smear negative, culture positive patients as 14.1% compared with the 34.7% of smear positive cases at the end of 18 month follow up.

With the use of Fibreoptic bronchoscopy (FOB), diagnosis of PTB in sputum smear negative retreatment

patients has become possible. The advantage with this instrument was the ability to visualize the bronchial tree and collect samples directly from the abnormal bronchial site.

Even though FOB procedures have some risk of complications like hemoptysis & Pneumothorax, it was considered to be a relatively safe procedure[25]. In our study, no one got any complication.

Number of previous studies shows, the positivity of Bronchial aspiration (BA) varies from 13% [26]to 61%. [27] Danek et al [28.] observed BA smear positive in 24% cases while So et al. [29] obtained a positive yield of 38% in bronchial aspirate.

Anand reported the diagnostic yield of BA smear to be 28%, BA culture to be 32%.

In our study bronchial wash AFB smear positive in 26.92% cases(14/52) and bronchial wash for AFB culture positive in 44.23%(23/52).

Thus the data generated in our study is comparable to previous studies.

In various other previous studies, Post bronchoscopy smear revealed AFB positivity ranging from 23% to 37%. 21% was noted by Danek et al., [28] 28% by Anand et al., [30] 35% by Wallace et al.,[26] 23% by Kulpati et al. [31]and 26% by Purohit et al 37% by So et al.[29]

In our study post bronchoscopy sputum is positive in 11.53% (6/52).

Bronchial brush for AFB smear is positive in 23% (12/52).

In bronchial wash, Bacterial culture diagnosed 23% (12/52) pyogenic infections. In which Pseudomonas 4/12, Streptococcus pyogenes 3/12, Klebsiella 2/12, Staph aureus 2/12, Moraxella 1/12. Early treatment of these patients, to prevent spread of the infection to community.

Bronchial wash for cytology shows acute inflammatory pathology in 76.92% (40/52) and bronchial brush for cytology shows 71.15% (37/52) of acute inflammatory pathology.

Importantly bronchial brush cytology shows malignancy in 2/52 patients (3.84%). In which 1 patient diagnosed as adeno carcinoma, another patient diagnosed as squamous cell carcinoma.

Pre bronchoscopy sputum for LPA detected m. tuberculosis in 15/52 (28.84%) patients (in this 15 patients, 5 patients LPA positive, 10 patients LPA negative, culture positive). In 14 patients sensitive to INH AND RIF, 1 patient was diagnosed as MDR TB.

Compared to pre FOB sputum for LPA (including LPA positive, culture positive) with FOB wash for AFB culture revealed better yield(p value <0.001) in the later group.

All pre FOB sputum for LPA positive patients (including culture positive) were within the margin of FOB wash for AFB

culture positive patients, except one patient whose pre FOB sputum for LPA positive but bronchial wash for AFB culture negative. That is if FOB washes for AFB culture is negative, LPA of pre bronchoscopy sputum is also negative (LPA negative and culture negative) (p value <0.001).

So fibreoptic broncoscopy is an excellent tool for diagnosis of smear negative pulmonary tuberculosis in retreatment patients.

CONCLUSION

Major advantage of bronchoscopy in smear negative retreatment pulmonary tuberculosis is, isolation of mycobacteria at an early stage when the destruction of lung parenchyma is minimal and the risk of spreading the disease to contact person can be decreased by early diagnosis and treatment.

The study concludes that flexible fibreoptic bronchoscopy was a useful tool in diagnosis of sputum smear negative retreatment pulmonary tuberculosis patients. Bronchoscopy revealed a higher bacteriological confirmation of diagnosis in patients with strong radiological and clinical evidence suggestive of actives pulmonary tuberculosis.

It also decides CAT II ATT in these patients, and it also diagnoses non tuberculous pathology like malignancy.

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ANNEXURE

INSTITUTIONAL ETHICAL COMMITTEE, STANLEY MEDICAL COLLEGE, CHENNAI-1

Title of the Work : Role of Fiberoptic bronchoscopy in smear negative retreatment pulmonary tuberclulosis.

Principal Investigator : Dr. S Navaneetha Krishnan

Designation : PG in MD (TB & RD)

Department : Department of TB & RD
Government Stanley Medical College,
Chennai-01

The request for an approval from the Institutional Ethical Committee (IEC) was considered on the IEC meeting held on 11.02.2014 at the Council Hall, Stanley Medical College, Chennai-1 at 2PM

The members of the Committee, the secretary and the Chairman are pleased to approve the proposed work mentioned above, submitted by the principal investigator.

The Principal investigator and their team are directed to adhere to the guidelines given below:

1. You should inform the IEC in case of changes in study procedure, site investigator investigation or guide or any other changes.
2. You should not deviate from the area of the work for which you applied for ethical clearance.
3. You should inform the IEC immediately, in case of any adverse events or serious adverse reaction.
4. You should abide to the rules and regulation of the institution(s).
5. You should complete the work within the specified period and if any extension of time is required, you should apply for permission again and do the work.
6. You should submit the summary of the work to the ethical committee on completion of the work.

MEMBER SECRETARY,
IEC, SMC, CHENNAI

PROFORMA

- NAME :
- AGE/SEX :
- IP NO :
- OP NO :
- PREVIOUS HISTORY OF TUBERCULOSIS TREATMENT :
- IF YES, NUMBER OF TIMES OF TREATMENT :
- DURATION OF TREATMENT :
- TREATMENT OUTCOME :
- INITIAL SPUTUM SMEAR FOR AFB :
- FOB DATE / FOB NO / SLIDE NO :
- BRONCHIAL WASH FOR AFB :
- BRONCHIAL WASH FOR AFB CULTURE AT GHTM :
- BRONCHIAL WASH FOR BACTERIAL C/S :
- BRONCHIAL WASH FOR CYTOLOGY :
- BRONCHIAL BRUSH FOR AFB SMEAR :
- BRONCHIAL BRUSH FOR CYTOLOGY :
- POST FOB SPUTUM SMEAR FOR AFB :
- LPA OF PRE FOB SPUTUM :

CONSENT FORM

I Mr / Mrs / Miss / _____ have understood the procedure read by the Doctors. I in my whole conscious awareness give consent for the procedure. I understand that the procedure is done in good faith for the best therapeutic results possible. I fully understand the consequences of the procedure. I can resign from the study at any point of time.

Signature

Name :

Date and Time :

Signature of Researcher :

சுயஒப்புதல்படிவம்

ஆய்வுசெய்யப்படும்தலைப்பு:

சளிகிருமி இல்லாத காசநோய் நோயாளிகளில் மூச்சுகுழாய் உள்நோக்கியின் பயன்பாடு பற்றியஆய்வு.

ஆராய்ச்சிநிலையம்: அரசுநெஞ்சகநோய் மருத்துவமனை , தாம்பரம்சானடோரியம், சென்னை.

பங்குபெறுபவரின்பெயர்:

பங்குபெறுபவரின்எண் :

பங்குபெறுபவர் ( ) இதனைக்குறிக்கவும் :

மேலேகுறிப்பிடப்பட்டுள்ள ஆய்வின்விவரங்கள்எனக்குவிளக்கப்பட்டது. என்னுடையசந்தேகங்களைக்கேட்கவும், அதற்க்கானதகுந்தவிளக்கங்களைப்பெறவும்வாய்ப்பளிக்கப்பட்டது.நான்இவ்வாய்வில்தன்னிச்சையாகத்தான் பங்கேற்கிறேன்.எந்தகாரணத்தினாலோஎந்தகட்டத்திலும்எந்தசட்டச்சிக்கலுக்கும்உட்படாமல்நான் இவ்வாய்வில் இருந்துவிலகிக் கொள்ளலாம்என்றும்அறிந்துகொண்டேன். ☐

இந்தஆய்வுசம்பந்தமாகவோ,இதைச்சார்ந்தமேலும்ஆய்வுமேற்கொள்ளும்போதும் இந்தஆய்வில்பங்குபெறும்மருத்துவர்என்னுடையமருத்துவஅறிக்கையைபார்ப்பதற்குஎண் அனுமதிதேவையில்லைஎனஅறிந்துகொள்கிறேன்.நான் ஆய்வில் இருந்துவிலகிக்கொண்டாலும்இதுபொருந்தும்எனஅறிகிறேன். ☐

இந்தஆய்வுமூலம்கிடைக்கும்தகவல்களையும்பரிசோதனைமுடிவுகளையும்மற்றும் சிகிச்சைதொடர்பானதகவல்களையும்மருத்துவர்மேற்க்கொள்ளும்ஆய்வில்பயன்படுத்திக் கொள்ளவும்அதைப்பிரசுரிக்கவும்எண் முழுமனதுடன்சம்மதிக்கிறேன . ☐

இந்தஆய்வில்பங்குகொள்ளஒப்புக்கொள்கிறேன்.எனக்குக்கொடுக்கப்பட்டஅறிவுரைப்படிநடந்துகொள்வதுடன்இந்தஆய்வைமேற்கொள்ளும்மருத்துவஅணிக்குஉன்னமையுடன்இருப்பேன்என்றுஉறுதிஅளிக்கின்றேன்.என்உடல்நலம்பாதிக்கப்பட்டாலோஅல்லதுஎதிர்பாராதவழக்கத்திற்குமாறானநோய்க்குறிதென்பட்டாலோ உடனேஅதைமருத்துவஅணிக்குத்தெரிவிப்பேன்எனஉறுதிஅளிக்கிறேன் . ☐

பங்குபெறுபவரின்கையொப்பம் ---------- இடம் ---------- தேதி ----------கட்டைவிரல்ரேகை

பங்குபெறுபவரின் பெயர்மற்றும்விலாசம் ----------

----------ஆய்வாளரின்கையொப்பம் ----------இடம் ----------

தேதி ----------ஆய்வாளரின்பெயர் ----------

நோயாளிக்கானதகPவல்படிவம்

மதிப்பிற்குரிய ஐயா / அம்மையீர்,

உங்கள் விருப்பத்தின் பேரில் "சளிகிருமி இல்லாத காசநோய் நோயாளிகளில் மூச்சுகுழாய் உள்நோக்கியின் பயன்பாடு பற்றிய ஆய்வில்"பங்கேற்கும்படி அன்புடன் கேட்டுக்கொள்கிறோம். இந்த ஆய்வில் ஆரய்ச்சி நோக்கத்துக்காக தாங்கள்பரிசோதனைக்கு உட்படுத்தப்படுவீர்கள். தகுந்த சிகிச்சை தங்களுக்கு தொடங்கப்படும். தங்களுக்கு இந்த ஆய்வில் பங்கேற்க விருப்பம் இருந்தால் தாங்கள் அருள்கூர்ந்து ஒப்புதல் படிவத்தைப் படித்துப்பார்த்துக் கையொப்பம் இடும்படிக் கேட்டுக்கொள்கிறேன்.

S.NO.	NAME	AGE	SEX	NUMBER OF TREATMENT	TREATMENT OUT COME	INITIAL SPUTUM AFB SMEAR	FOB WASH FOR AFB	FOB WASH FOR AFB CULTURE	FOB BRUSH FOR AFB	POST FOB SPUTUM SMEAR FOR AFB	LPA INITIAL SPUTUM	FOB WASH FOR NTC / S	FOB WASH FOR CYTOLOGY	FOB BRUSH FOR CYTOLOGY
1	DHARANI	45YR	FM	1 TIME	DEFAULTER	NEGATIVE	POSITIVE 1+	POSITIVE	POSITIVE 1+	NEGATIVE	SENSITIVE TO INH,RIF	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
2	BASKARASAMY	24YR	FM	2 TIMES	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACELLULAR SMEAR	ACUTE INFLAMATORY PATHOLOGY
3	THIRUNAVUKARASU	53YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	NO SPECIFIC PATHOLOGY	NO SPECIFIC PATHOLOGY
4	RAVI	41YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACELLULAR SMEAR	ACUTE INFLAMATORY PATHOLOGY
5	GAJENDRAN	50YR	M	1 TIME	DEFAULTER	NEGATIVE	POSITIVE 2+	POSITIVE	POSITIVE 1+	NEGATIVE	SENSITIVE TO INH,RIF	NO GROWTH	ACELLULAR SMEAR	ACUTE INFLAMATORY PATHOLOGY
6	KUZHALANTHAIVEL	55YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	NO SPECIFIC PATHOLOGY	NO SPECIFIC PATHOLOGY
7	SHANTHI	30YR	FM	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	NO SPECIFIC PATHOLOGY	NO SPECIFIC PATHOLOGY
8	EGAMBARAM	34YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACELLULAR SMEAR	ACELLULAR SMEAR
9	MANIBALAN	39YR	M	2 TIMES	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	SUSPECIOUS MALIGNANCY SUGGEST FOLLOW UP
10	MANIVANNAN	56YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	PSEUDOMONUS	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
11	PERUMAL	54YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
12	DOSS	37YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
13	KUMAR	46YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE SCANTY	SENSITIVE TO INH,RIF	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
14	GAJENDRAN	65YR	M	1 TIME	DEFAULTER	NEGATIVE	POSITIVE SCANTY	POSITIVE	NEGATIVE	NEGATIVE	SENSITIVE TO INH,RIF	STAP AUREUS	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
15	GOVINDASAMY	63YR	M	1 TIME	DEFAULTER	NEGATIVE	POSITIVE 1+	POSITIVE	POSITIVE SCANTY	NEGATIVE	SENSITIVE TO INH,RIF	PSEUDOMONUS	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
16	SUBRAMANI	65YR	M	1 TIME	DEFAULTER	NEGATIVE	POSITIVE 1+	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	MORAXELLA	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
17	GOPAL	50YR	M	2 TIMES	CURED	NEGATIVE	POSITIVE 1+	POSITIVE	POSITIVE SCANTY	NEGATIVE	SENSITIVE TO INH,RIF	STREPTOCCUS PYOGENS	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
18	RAMASAMY	68YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY

19	SRINIVASAN	44YR	M	2 TIMES	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
20	KRISHNASWAMY	78YR	M	1 TIME	CURED	NEGATIVE	POSITIVE 1+	POSITIVE	NEGATIVE	NEGATIVE	SENSITIVE TO INH,RIF	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
21	BALAN	45YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	NO SPECIFIC PATHOLOGY
22	VIJAYAKUMAR	52YR	M	2 TIMES	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	NO SPECIFIC PATHOLOGY
23	MURUGESAN	51YR	M	2 TIMES	DEFAULTER	NEGATIVE	NEGATIVE	POSITIVE	POSITIVE	NEGATIVE	SENSITIVE TO INH,RIF	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
24	SARAVANAN	40YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	NO SPECIFIC PATHOLOGY
25	KAMAL	72YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	NO SPECIFIC PATHOLOGY
26	SANTHAKUMAR	35YR	M	2 TIMES	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	KLEBSILLA	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
27	SETTU	30YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	NO SPECIFIC PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
28	MURUGAN	35YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	NO SPECIFIC PATHOLOGY	NO SPECIFIC PATHOLOGY
29	PENSICAN	68YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	NO SPECIFIC PATHOLOGY	NO SPECIFIC PATHOLOGY
30	BALU	44YR	M	1 TIME	CURED	NEGATIVE	POSITIVE 1+	POSITIVE	POSITIVE 1+	NEGATIVE	SENSITIVE TO INH,RIF	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
31	MUNIYAPPAN	57YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
32	GENGAN	60YR	M	2 TIMES	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	KLEBSILLA	ACUTE INFLAMATORY PATHOLOGY	POSITIVE FOR MALIGNANCY-SQUAMUS
33	ELUMALAI	55YR	M	1 TIME	CURED	NEGATIVE	POSITIVE 1+	POSITIVE	POSITIVE 1+	POSITIVE 1+	SENSITIVE TO INH,RIF	STREPTOCCUS PYOGENS	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
34	RAJENDRAN	50YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
35	VENKADESAN	50YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	NO SPECIFIC PATHOLOGY
36	KUMAR	45YR	M	2 TIMES	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY

37	YOGALAXMI	16YR	FM	1 TIME	DEFAULTER	NEGATIVE	POSITIVE SCANTY	POSITIVE	POSITIVE SCANTY	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	NO SPECIFIC PATHOLOGY
38	SINGARAM	50YR	M	1 TIME	CURED	NEGATIVE	POSITIVE SCANTY	POSITIVE	POSITIVE 1+	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
39	GOVINDASAMY	65YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	NO SPECIFIC PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
40	KUPPAN	61YR	M	2 TIMES	CURED	NEGATIVE	POSITIVE 1+	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
41	MANI	60YR	M	2 TIMES	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
42	MANI	50YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
43	SEKAR	30YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
44	KARUPPAN	60YR	M	2 TIMES	DEFAULTER	NEGATIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE 2+	SENSITIVE TO INH,RIF	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
45	MANI	68YR	M	1 TIME	DEFAULTER	NEGATIVE	POSITIVE 1+	POSITIVE	POSITIVE 1+	POSITIVE 1+	SENSITIVE TO INH,RIF	NO GROWTH	NO SPECIFIC PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
46	DHANAKOTTI	80YR	M	1 TIME	CURED	NEGATIVE	POSITIVE 1+	POSITIVE	POSITIVE 1+	NEGATIVE	SENSITIVE TO INH,RIF	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
47	SHANKAR	40YR	M	2 TIMES	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	STAP AUREUS	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
48	BASKARAN	54YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	POSITIVE	NEGATIVE	POSITIVE 1+	SENSITIVE TO INH,RIF	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
49	PONNAN	55YR	M	1 TIME	CURED	NEGATIVE	NEGATIVE	POSITIVE	NEGATIVE	NEGATIVE	NEGATIVE	STREPTOCCUS PYOGENS	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
50	VISVANATHAN	78YR	M	2 TIMES	CURED	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NO GROWTH	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY
51	KUPPU	37YR	M	1 TIME	DEFAULTER	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	NEGATIVE	PSEUDOMONUS	ACUTE INFLAMATORY PATHOLOGY	NO SPECIFIC PATHOLOGY
52	KALYANAKUMAR	54YR	M	2 TIMES	CURED	NEGATIVE	NEGATIVE	POSITIVE	POSITIVE SCANTY	POSITIVE 1+	RESISTANT TO INH,RIF	PSEUDOMONUS	ACUTE INFLAMATORY PATHOLOGY	ACUTE INFLAMATORY PATHOLOGY

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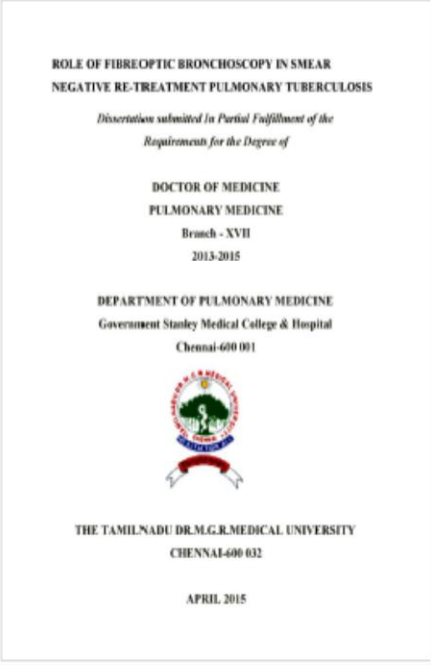

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Dissertation submitted In Partial Fulfillment of the Requirements for the Degree of

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